

0152
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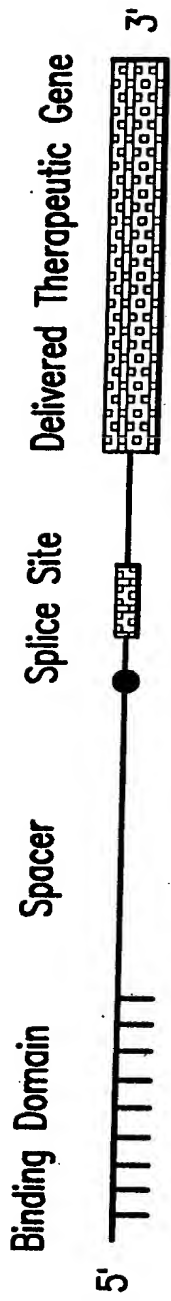
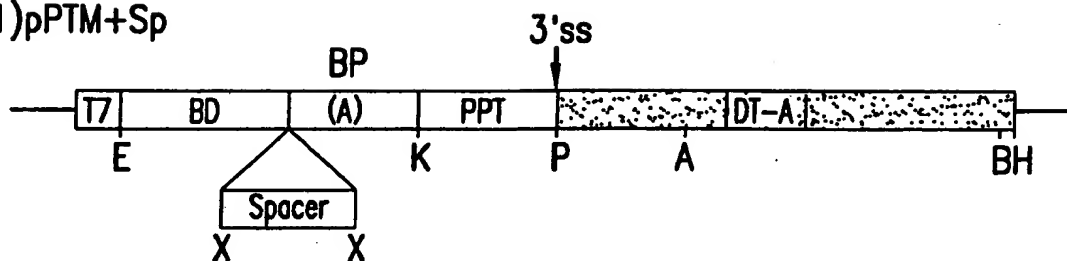


FIG.1A

151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934, 935, 936, 937, 938, 939, 940, 941, 942, 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956, 957, 958, 959, 960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, 980, 981, 982, 983, 984, 985, 986, 987, 988, 989, 990, 991, 992, 993, 994, 995, 996, 997, 998, 999, 1000

(1)pPTM+Sp



(2)pPTM+Sp

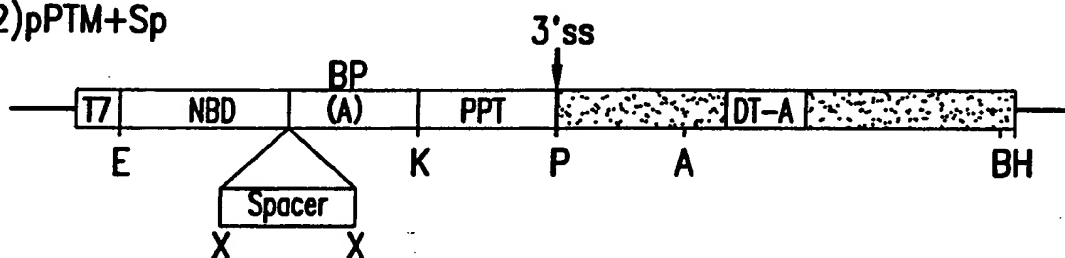


FIG.1B

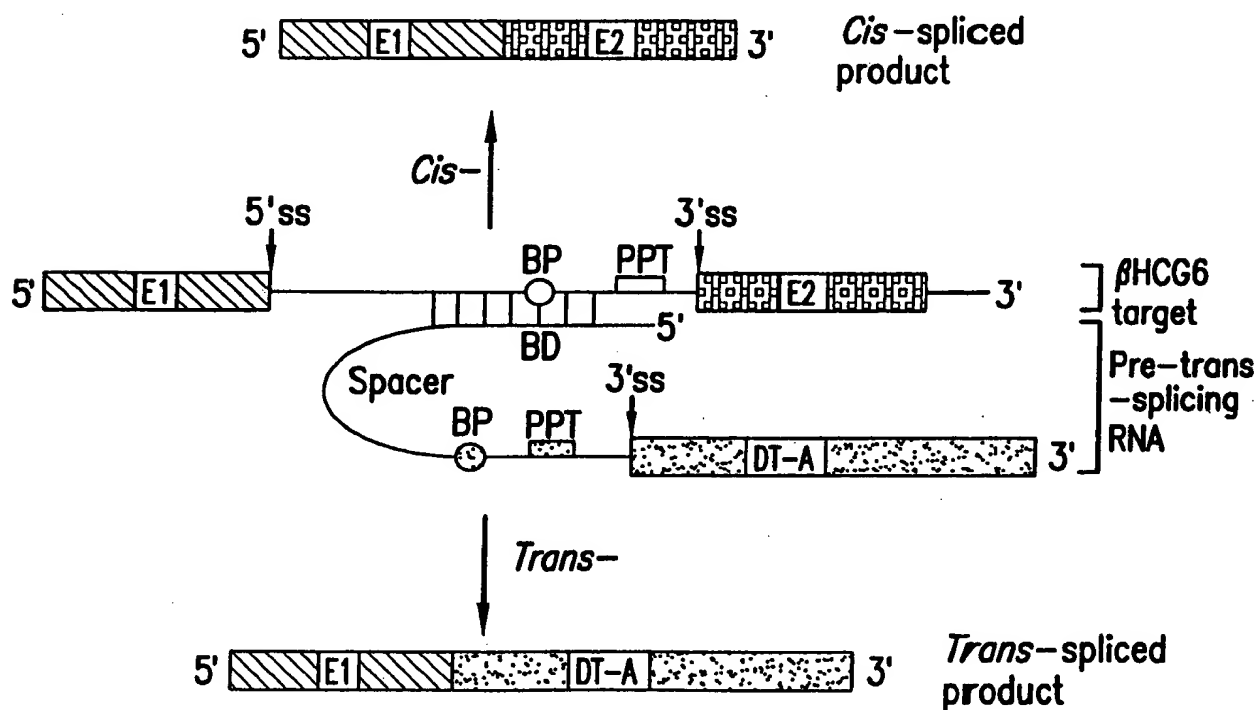


FIG.1C

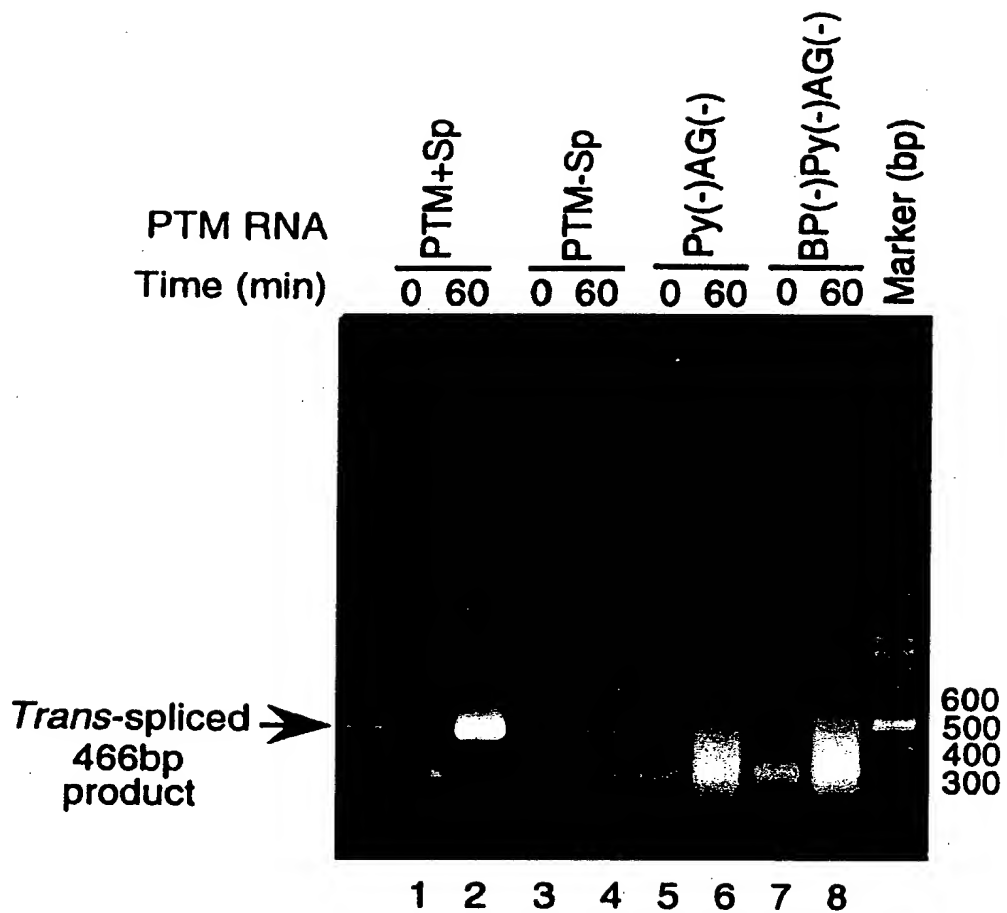


FIG.2A

10/17/03
11:11:18
10/17/03 11:11:18

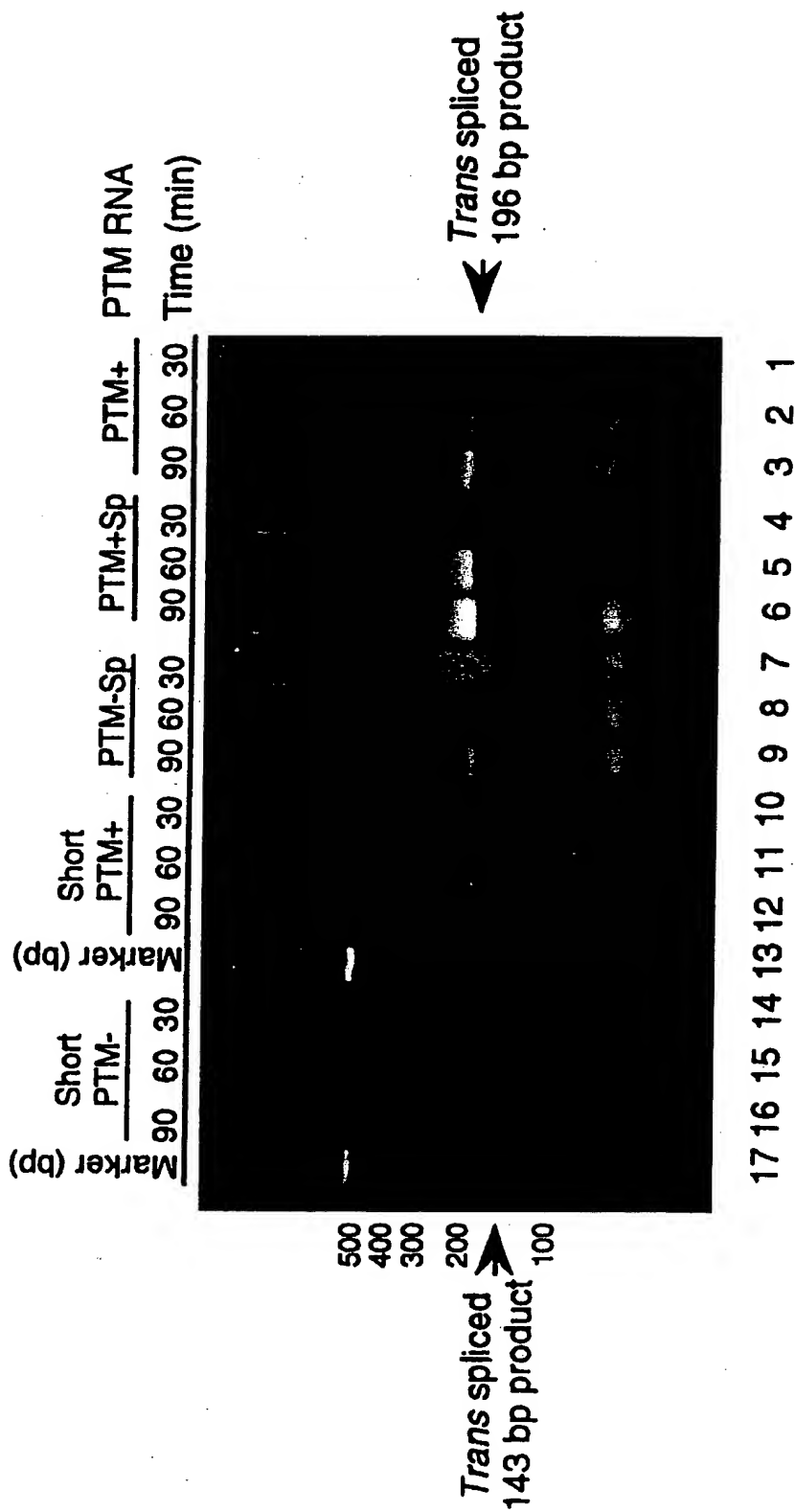


FIG.2B

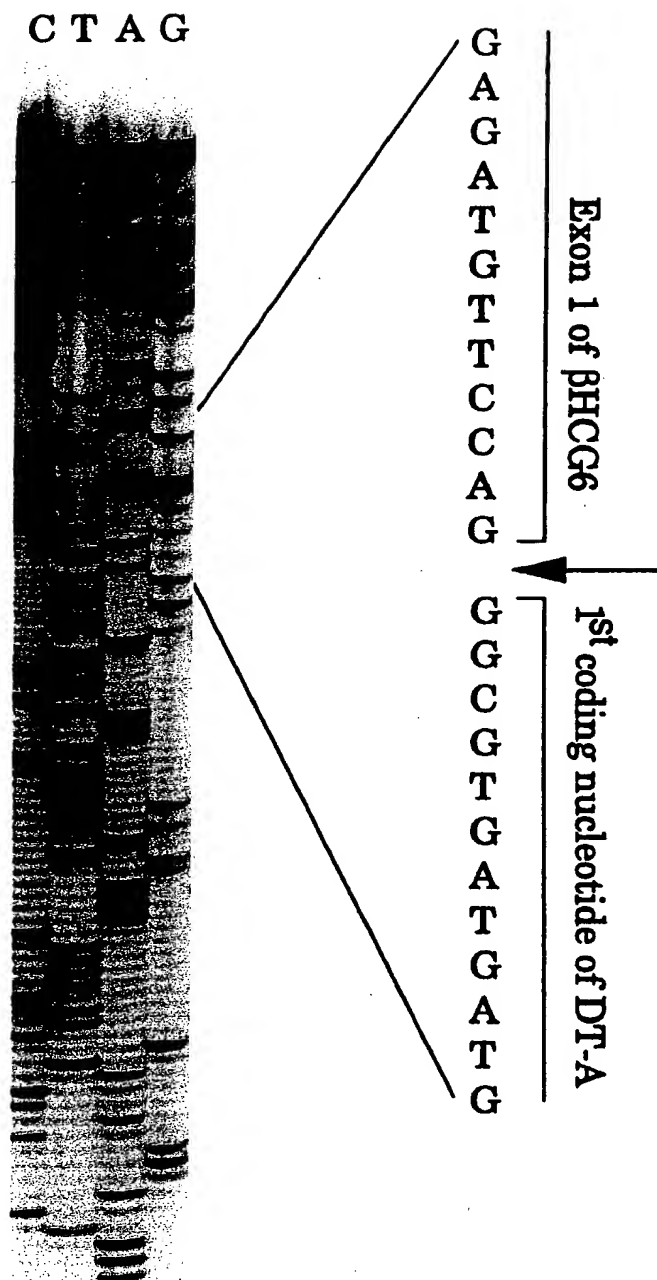
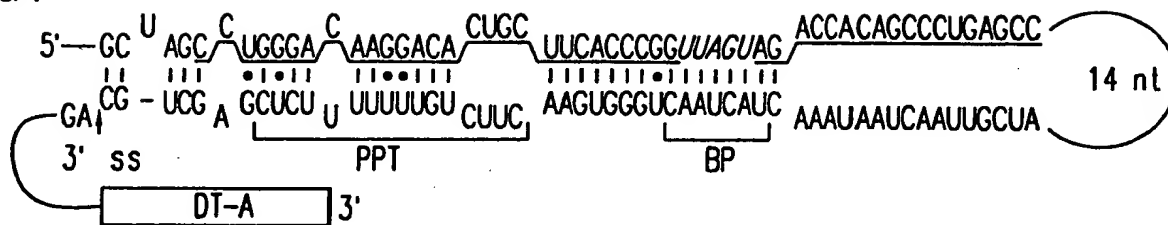
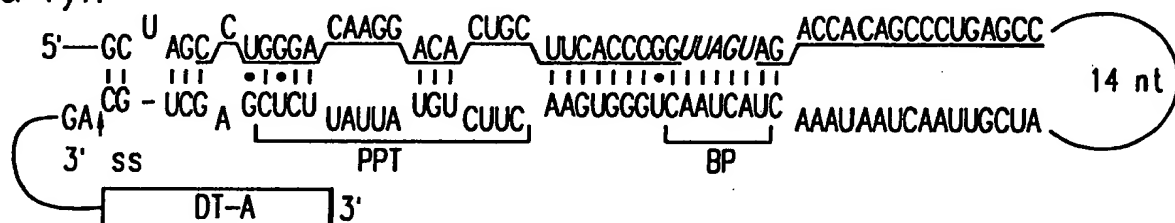


FIG.3

1. PTM+SF:



2. PTM+SF-Py1:



3. PTM+SF-Py2:

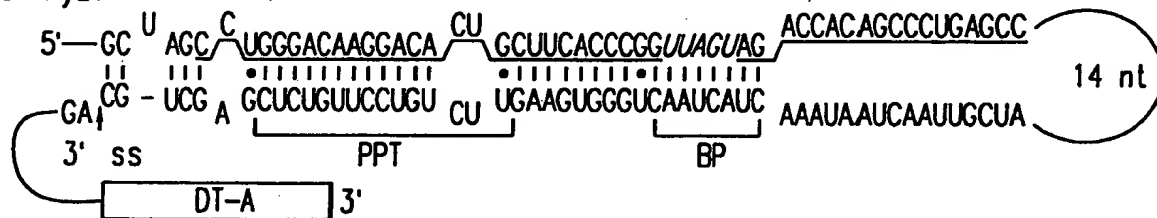


FIG.4A

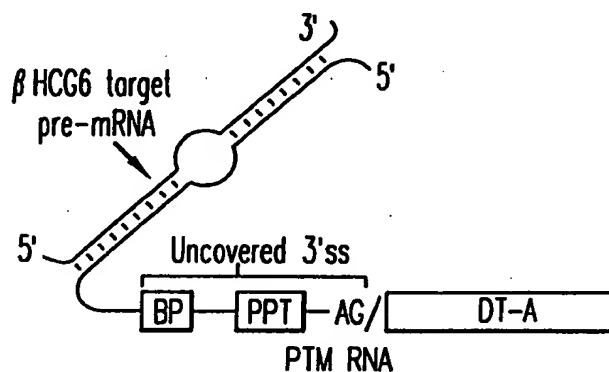


FIG.4B

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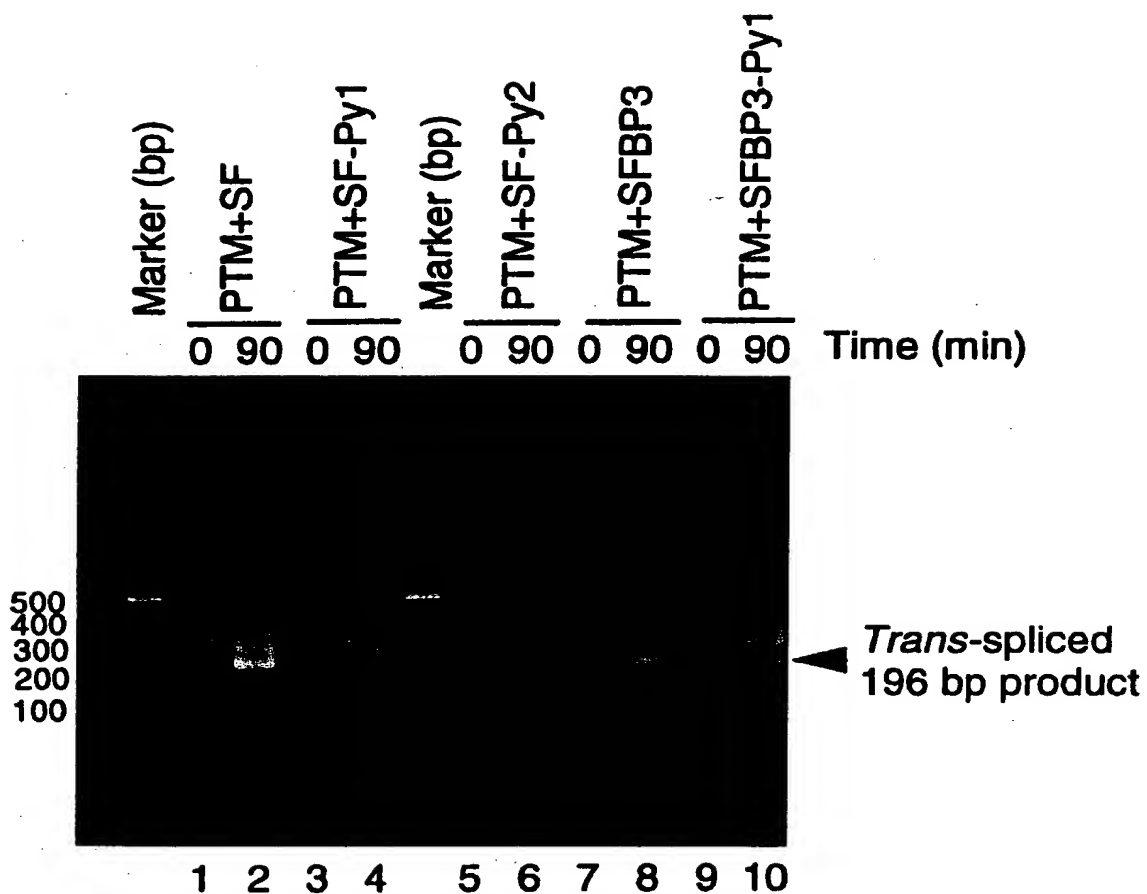


FIG.4C

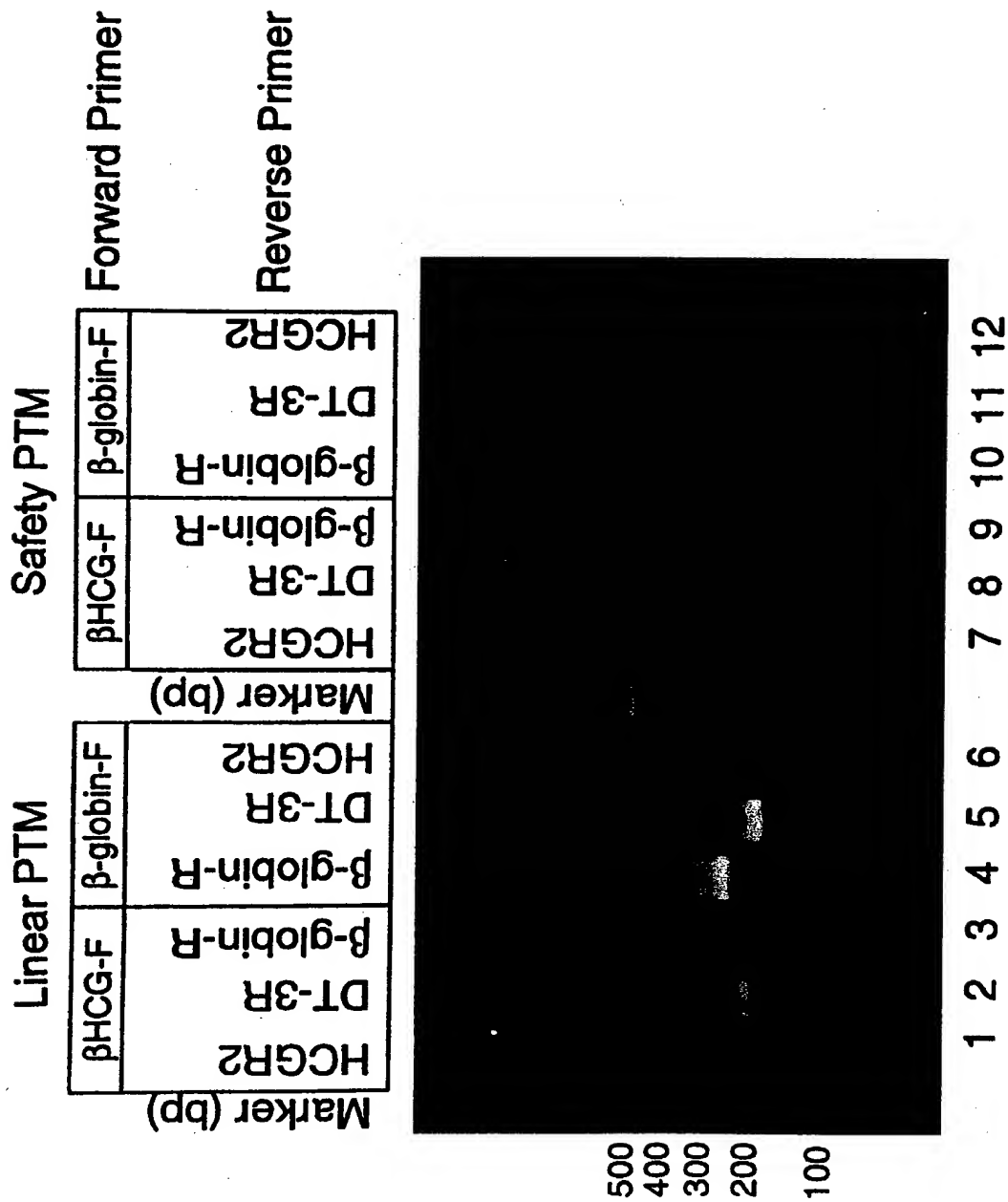


FIG.5

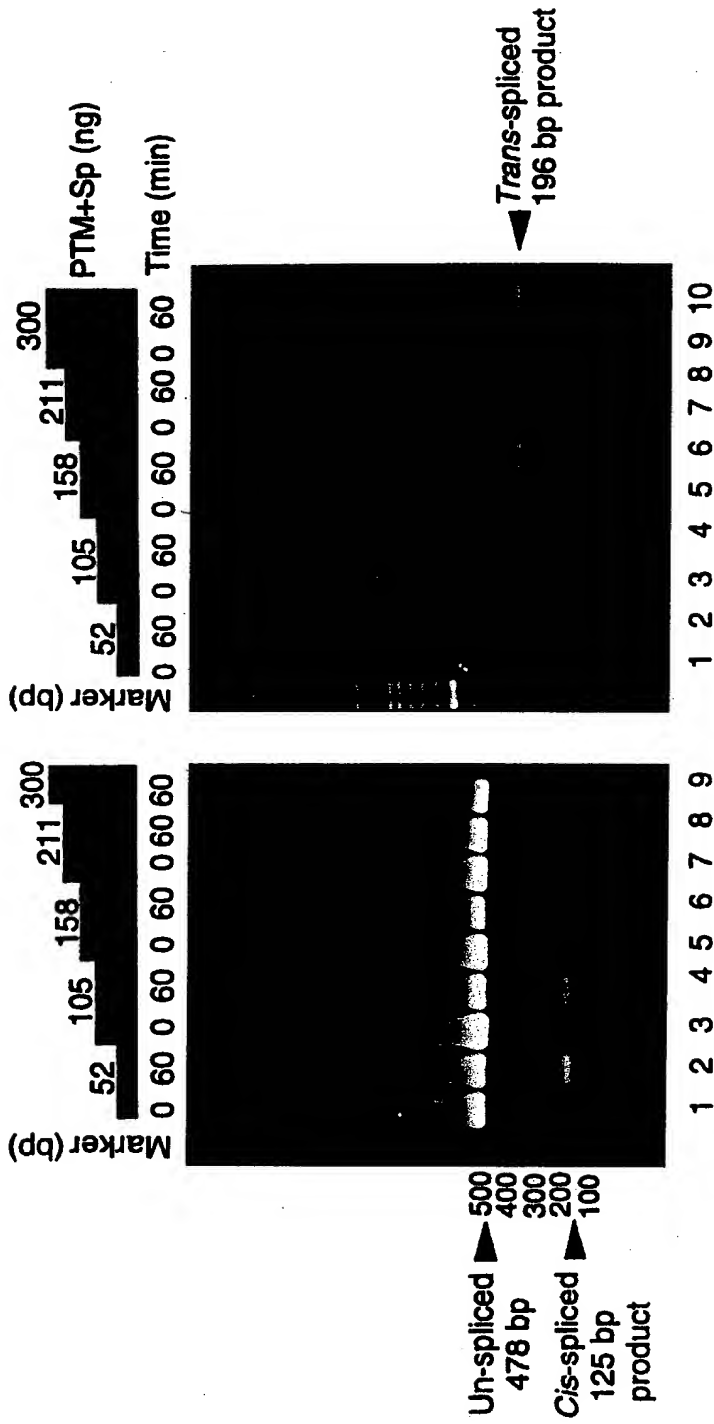


FIG. 6A

FIG. 6B

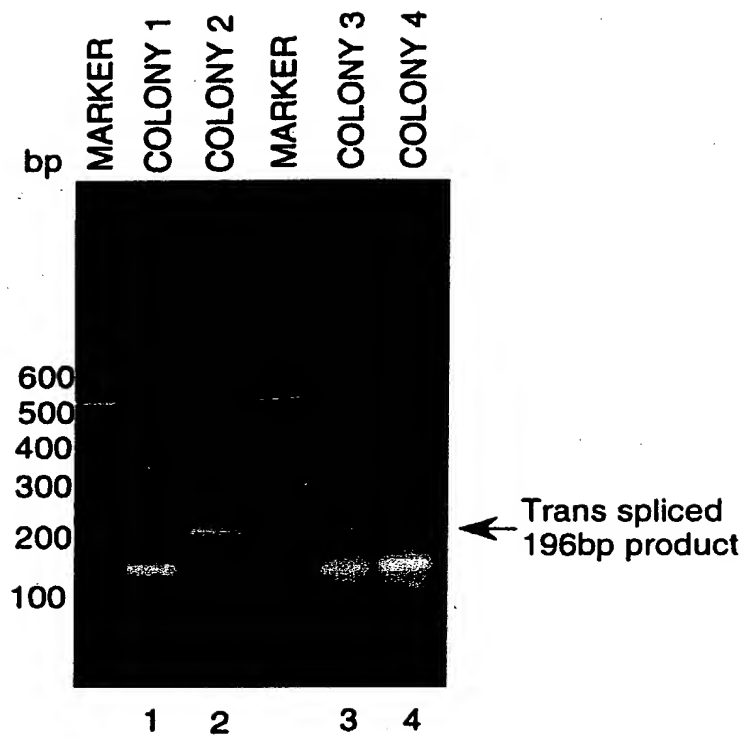


FIG.7A



EXON 1 OF β HCG6 ↓

5'-CAGGGACGCACCAAGGATGGAGATGTTCCAG-GGGCTGATGATGTTGTT

↓ 1ST CODING NUCLEOTIDE OF DT-A

GATTCCTTAAATCTTTTGTGATGGAACCTTTCTTCGTACCACGGGACTA

AACCTGGTTATGTAGATTCCATTCAAAA-3'

FIG.7B

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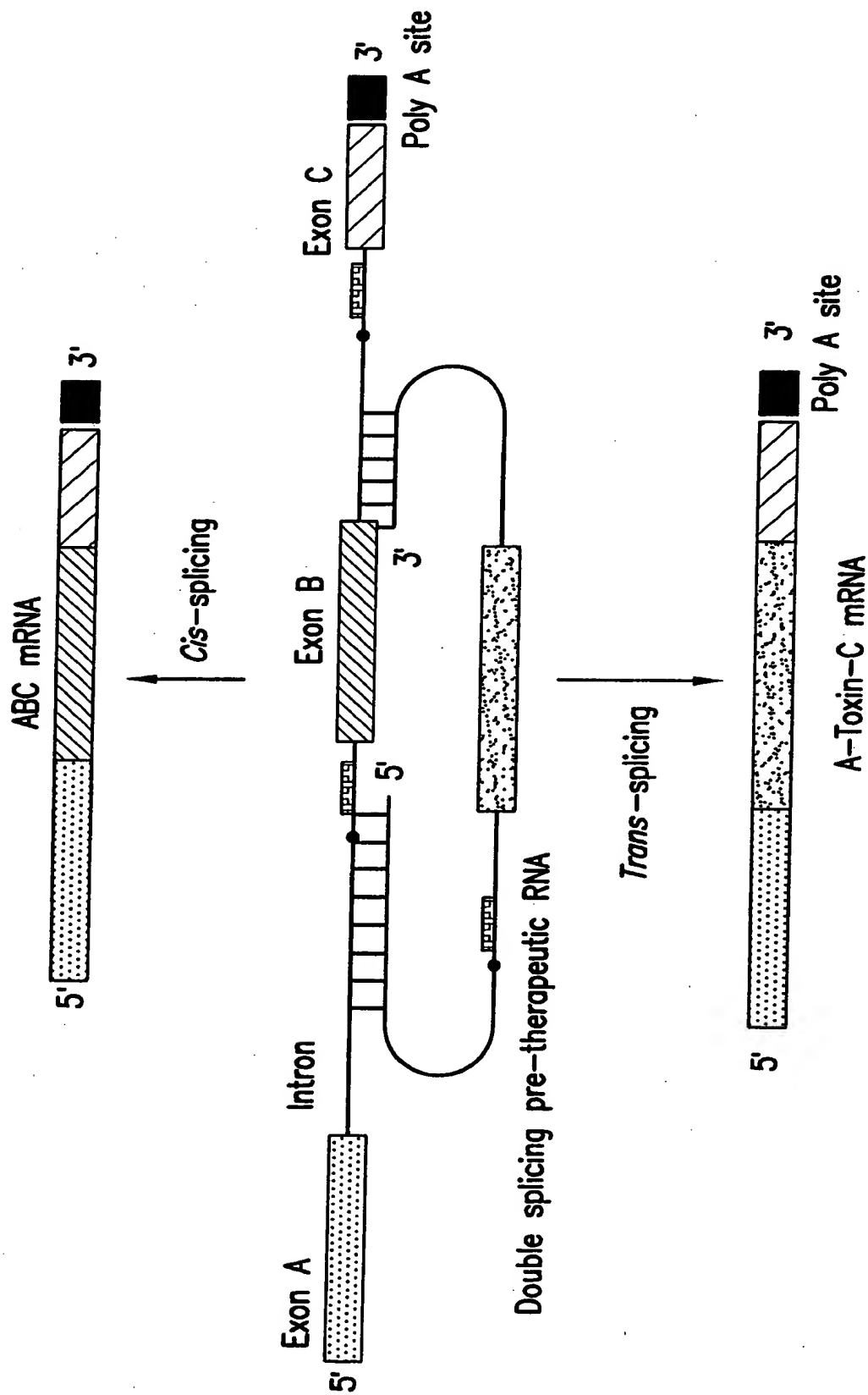


FIG.8A

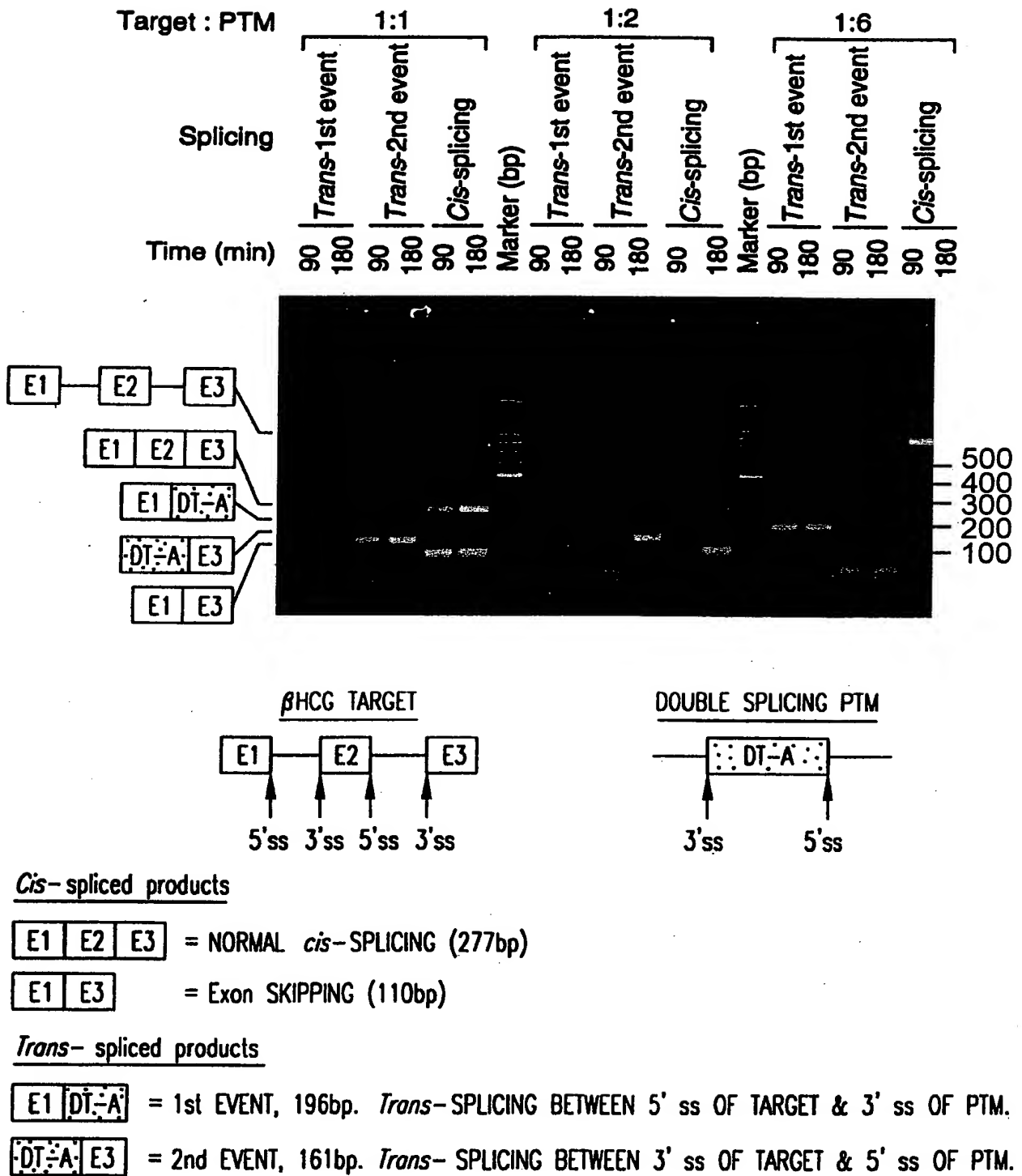


FIG.8B

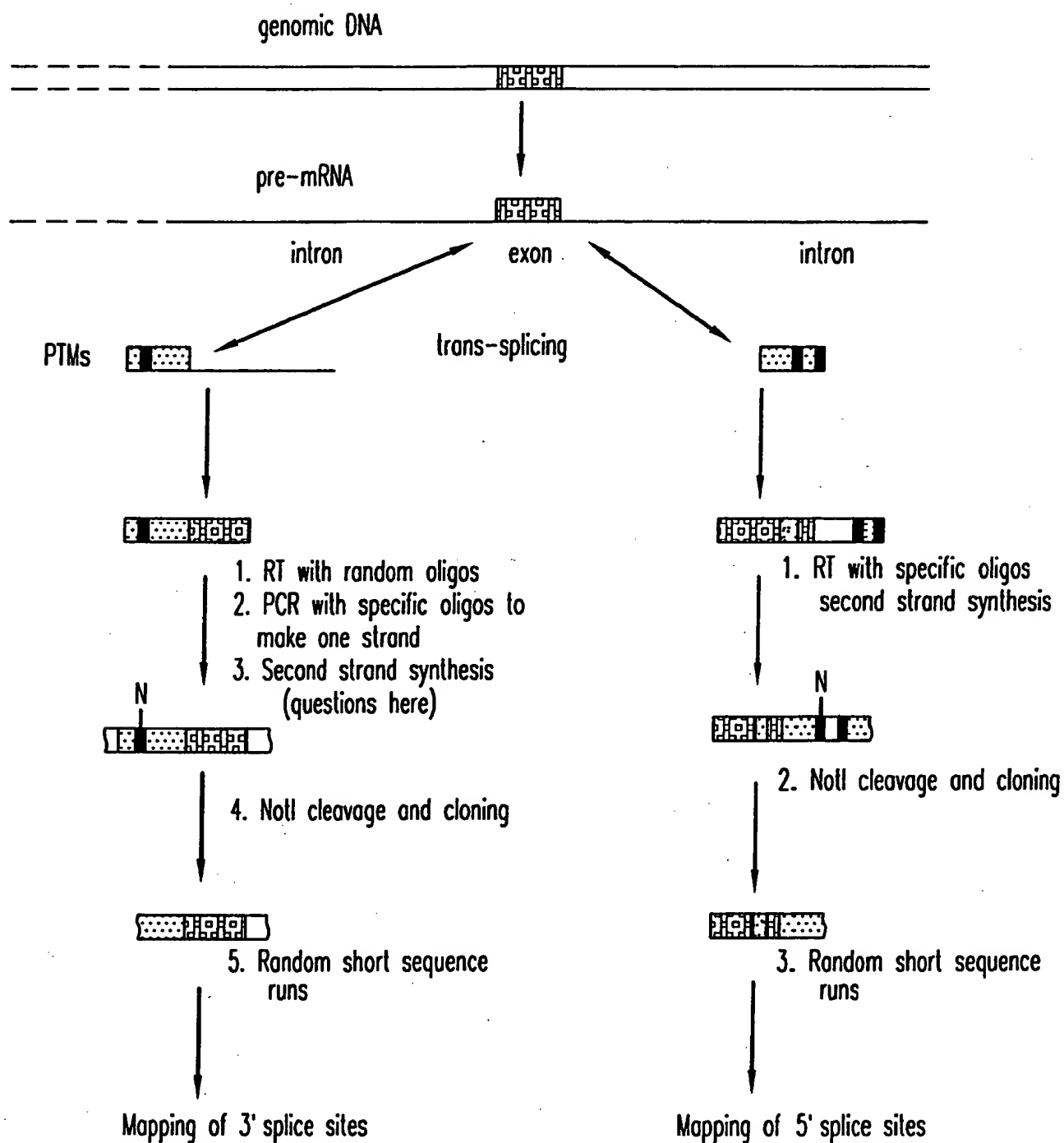
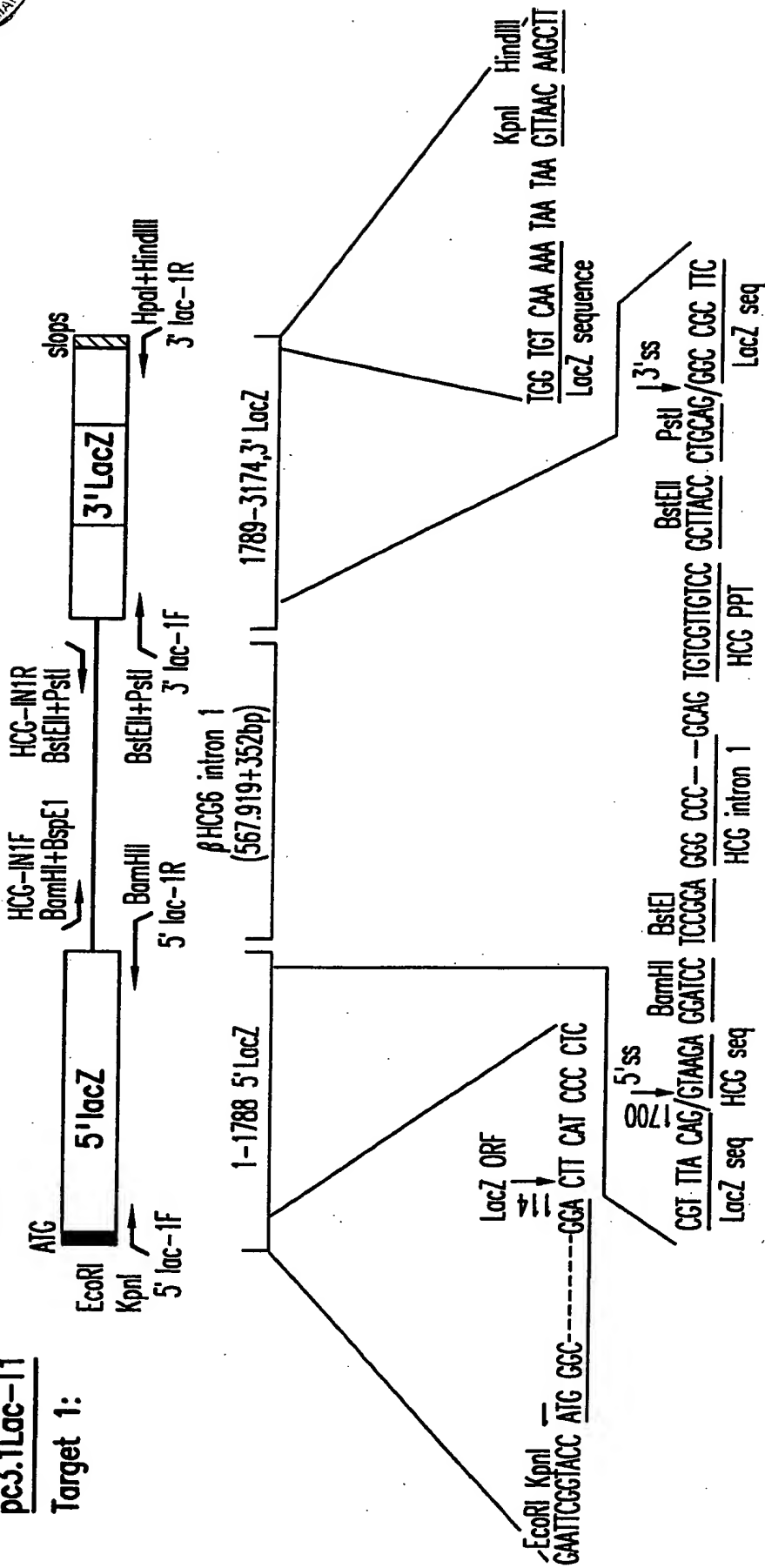


FIG.9

pc3.1Lac-T1

Target 1:



pc3.1PTM2:

FIG.10A

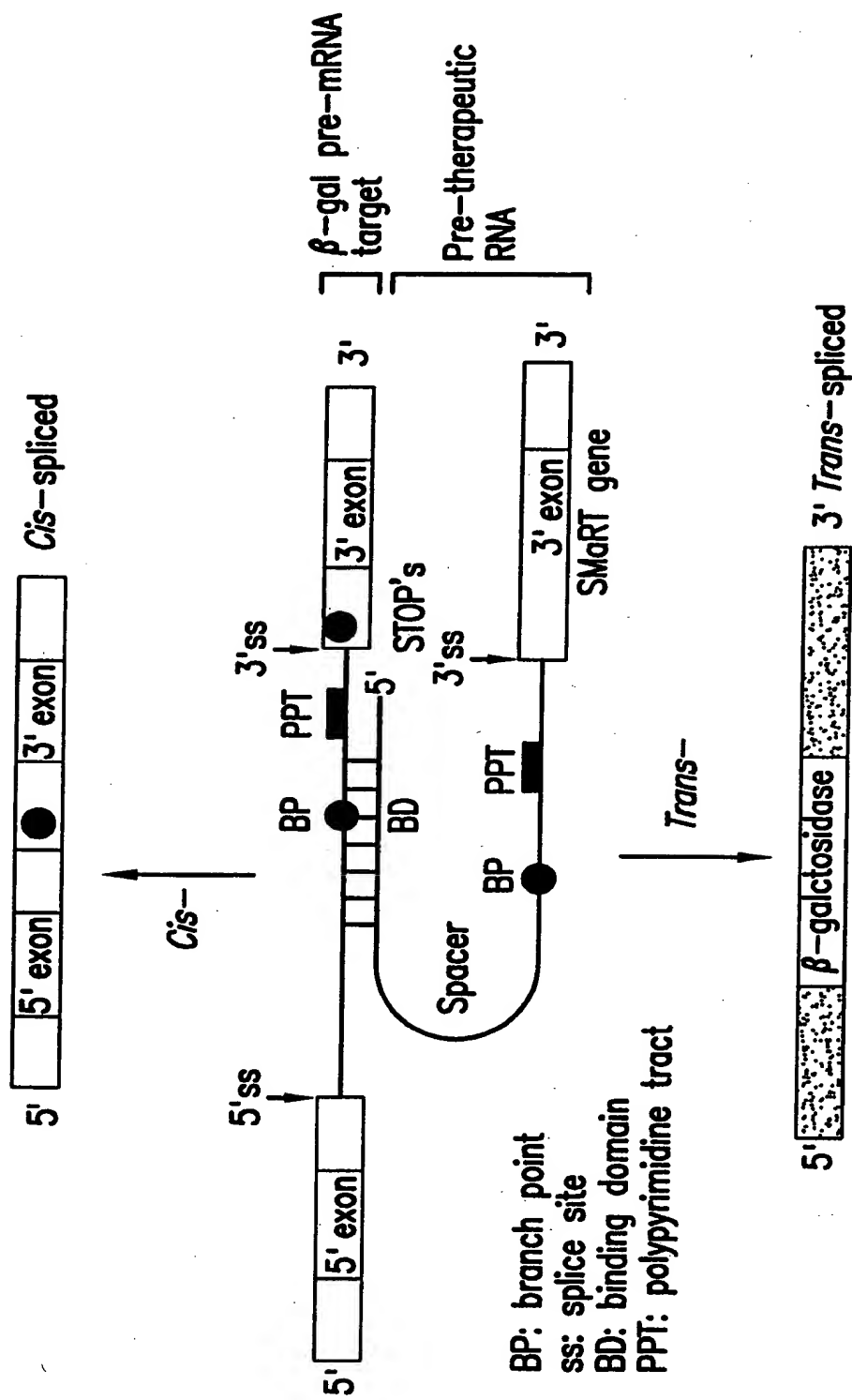


FIG.10B

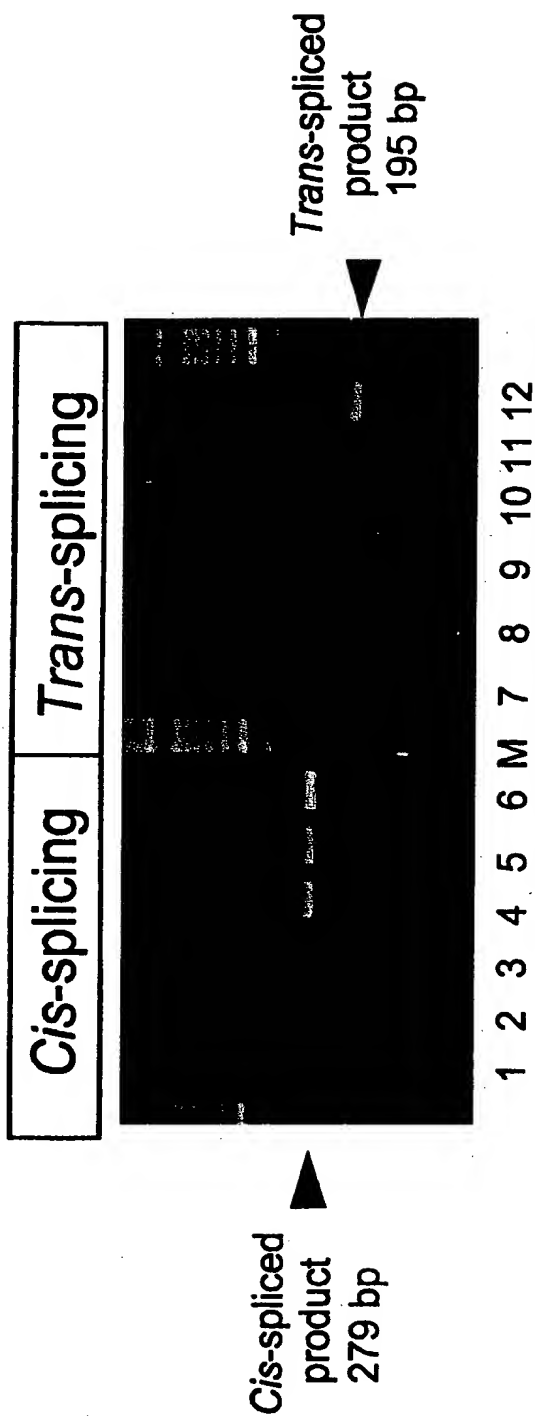


FIG.11A

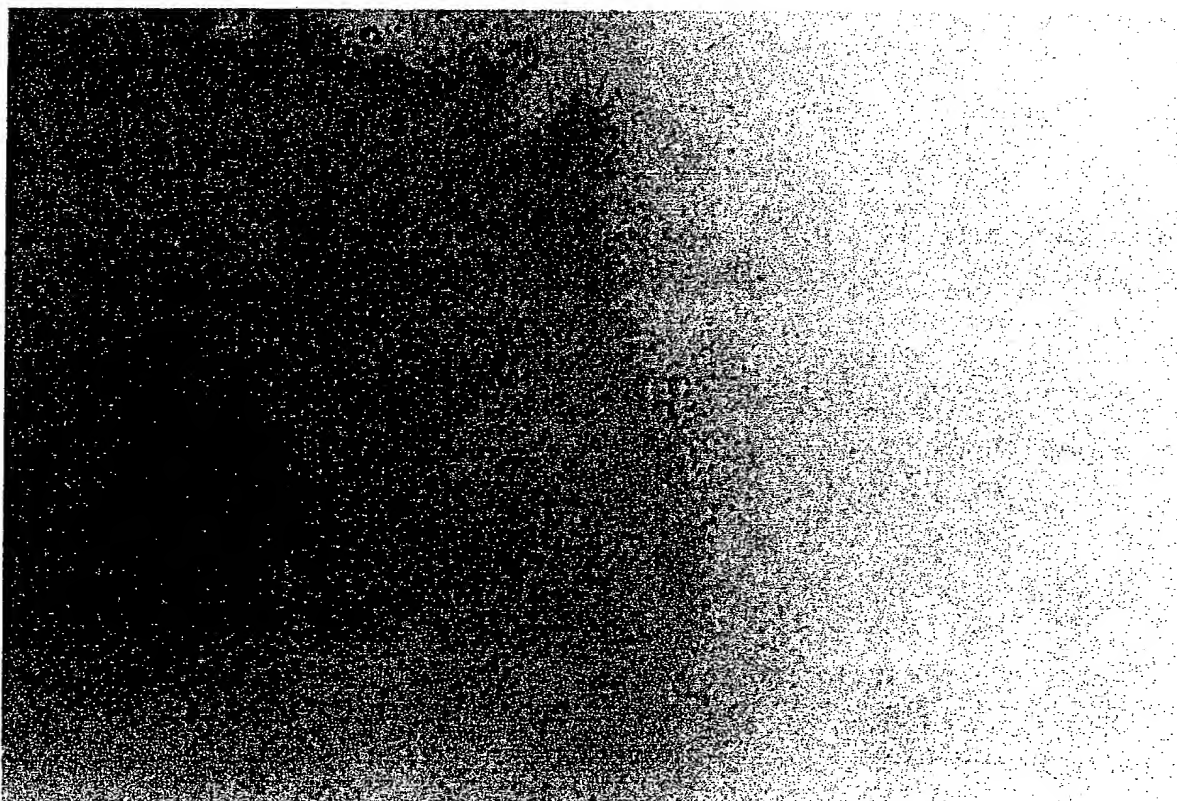


FIG.11B

EXHIBIT & TRADEMARK OFFICE
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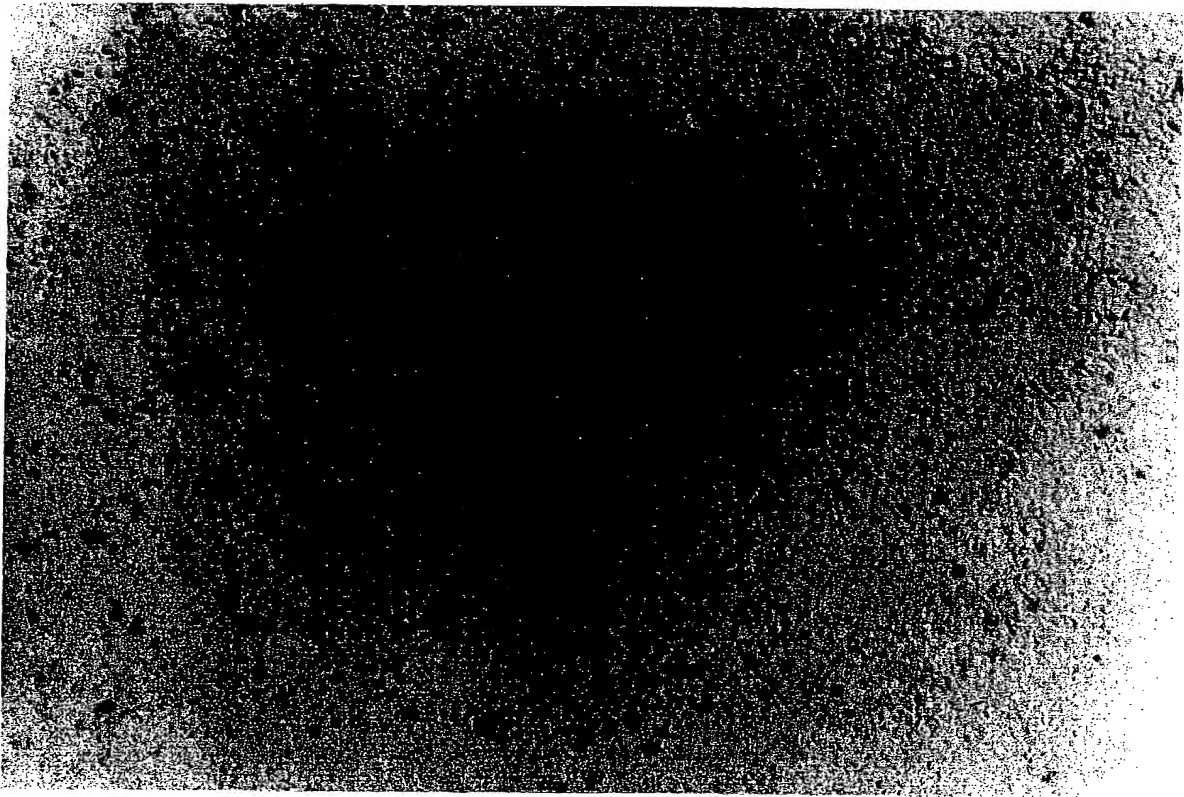


FIG.11C

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OIPK JC
COPY & TRADEMARK OFF

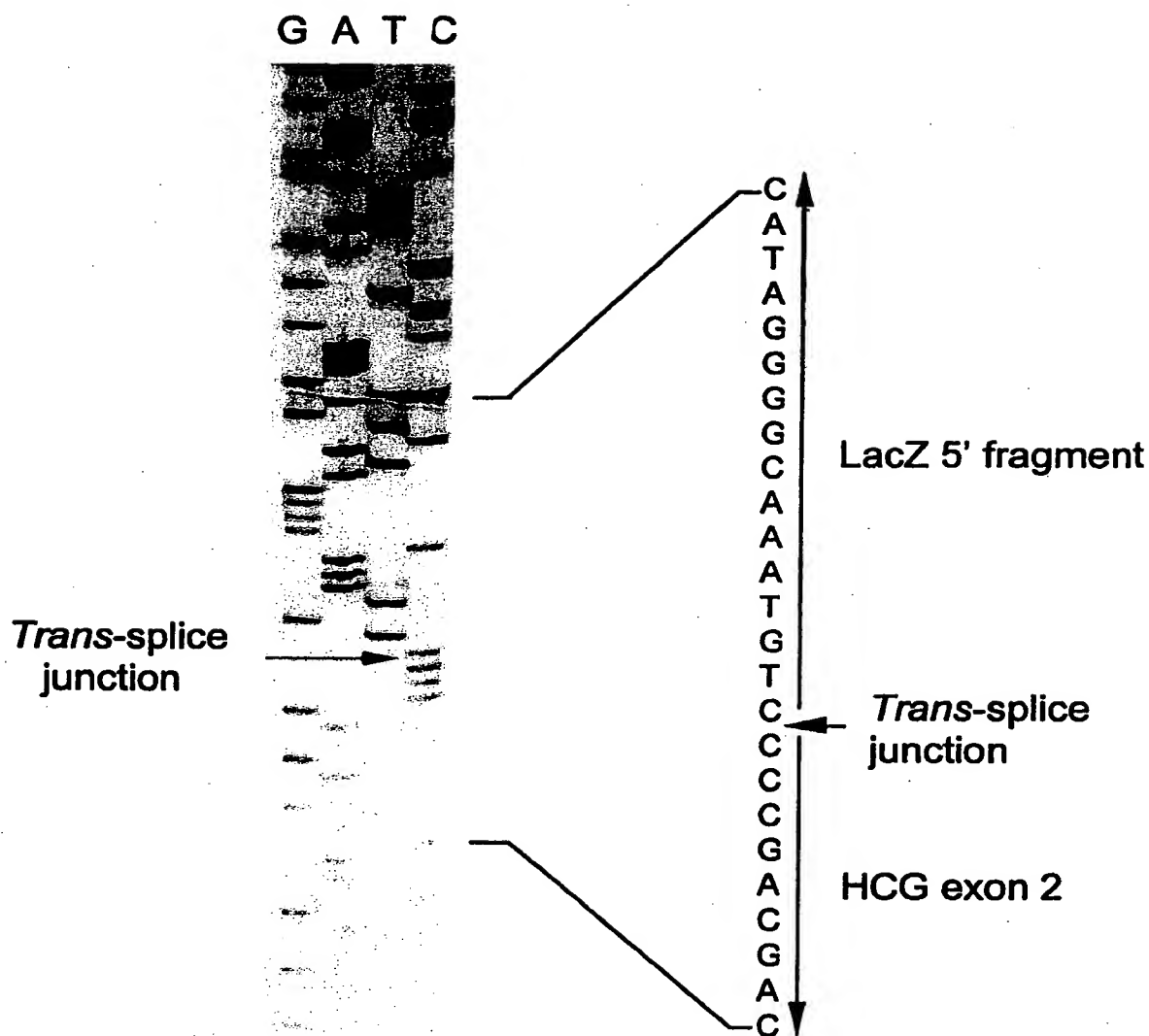


FIG.12A



1. NUCLEOTIDE SEQUENCES OF THE *cis*-SPICED PRODUCT (285 bp):

BioLac-TR1

GGCTTCGCTACCTGGAGAGACGCCCGCTGATCCTTTGCGAATACCCACGCCGATGGTAACAGTCTTG

Splice junction

GGCGTTTCGCTAAATACTGGCAGCGGTTTCGTCAGTATCCCGTTTACAG/GGCGGCTTCGCTCTAATAATG

GGACTGGGTGATCAGTCGCTGATTAAATATGATGAACAACGCCGTCGGCTTACGGCGGTGATTT

Lac-TR2

TGGCGATACCGGAACGATCGCCAGTTCCTGATGAACGGTCTGGTCTTTGCGACCGCACGCCGATCCAG

2. NUCLEOTIDE SEQUENCES OF THE *trans*-SPICED PRODUCT (195 bp)

BioLac-TR1

GGCTTCGCTACCTGGAGAGACGCCCGCTGATCCTTTGCGAATACCCACGCCGATGGTAACAGTCTTGG

Splice junction

CGGTTTCGCTAAATACTGGCAGCGGTTTCGTCAGTATCCCGTTTACAG/GGGCTGCTGCTGTTGCTGCTGCT

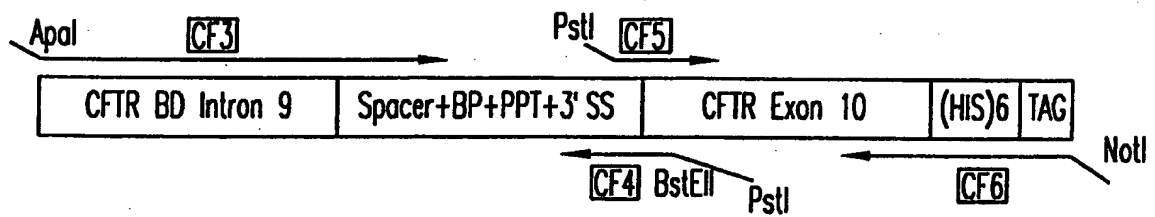
HCCR2

GAGCATGGCGGGACATGGGCATCCAAAGGAGCCACTTCGGCCACGGTGCCG

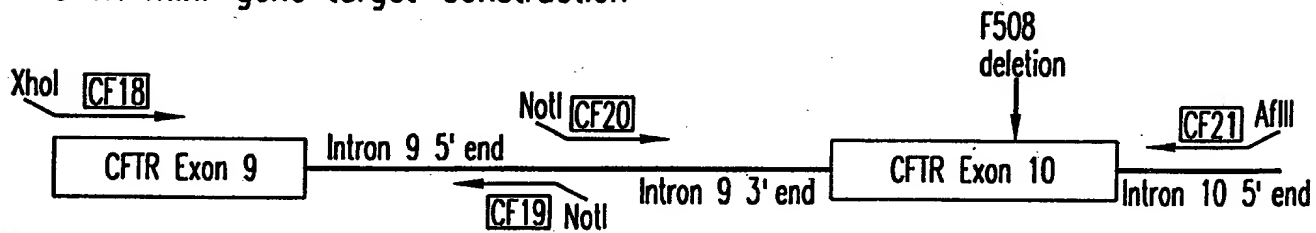
FIG.12B



CFTR Pre-therapeutic molecule (PTM or "bullet")



CFTR mini-gene target-construction



Trans-splicing Repair

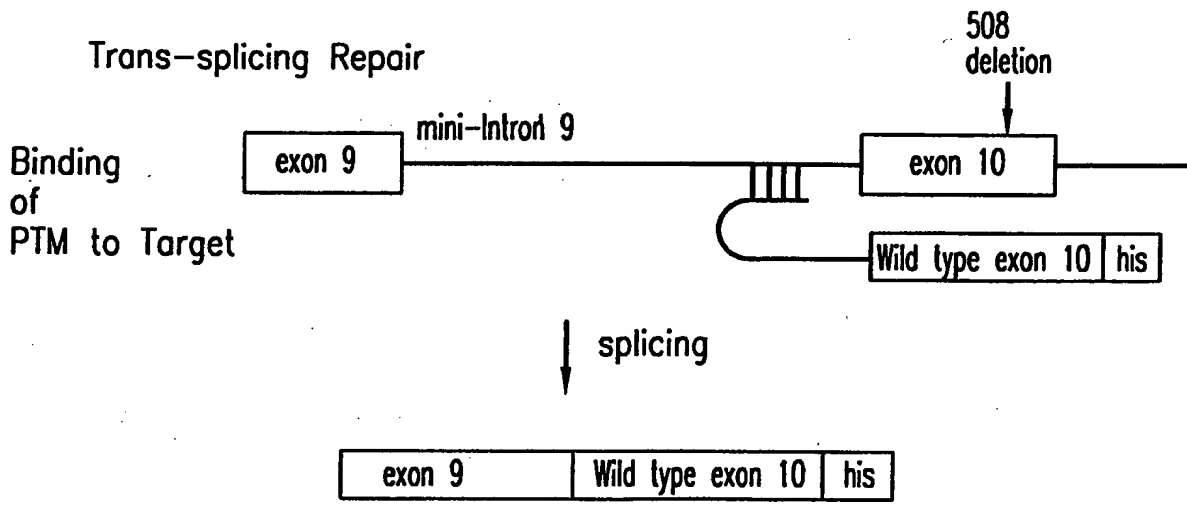


FIG.13

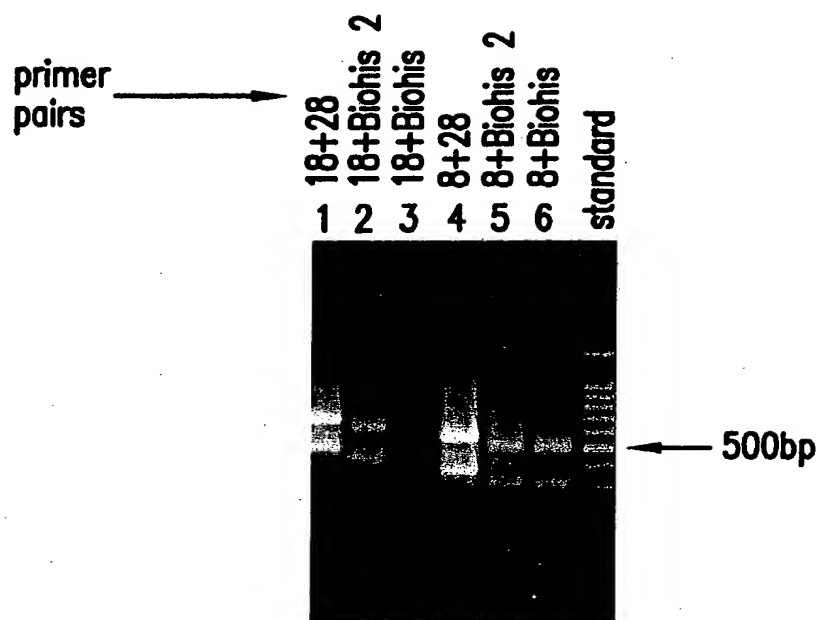
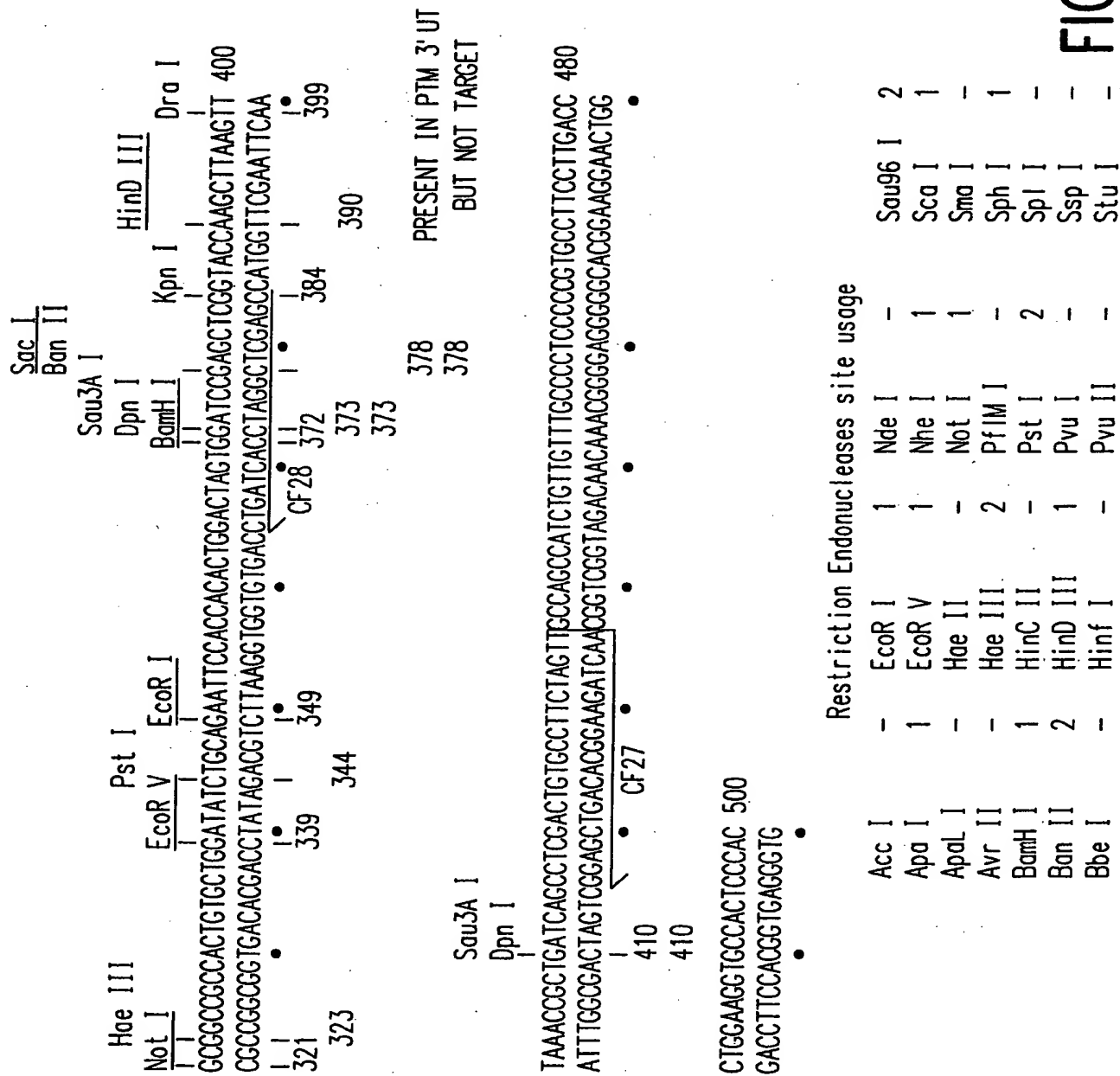


FIG.14

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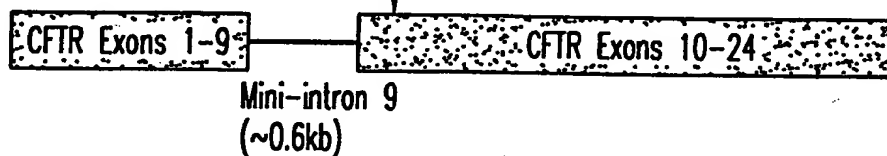
FIG. 15A





PTM [CFTR BD Intron 9] [Spacer+BP+PPT+3' SS] [CFTR exons 10-24] [(His) 6] TAG

CFTR Target
(mini-gene)



Cotransfect PTM and target molecules in HEK 293 cells
and detect repaired CFTR mRNA by RT-PCR.

Repaired
CFTR mRNA

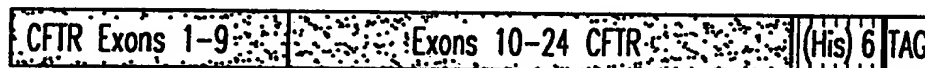


FIG.16

Double Splicing PTM

CFTR BD intron 9	Spacer+BP+PPT+3'SS	CFTR exon 10	Spacer+BP+PPT+5'SS	CFTR BD intron 10
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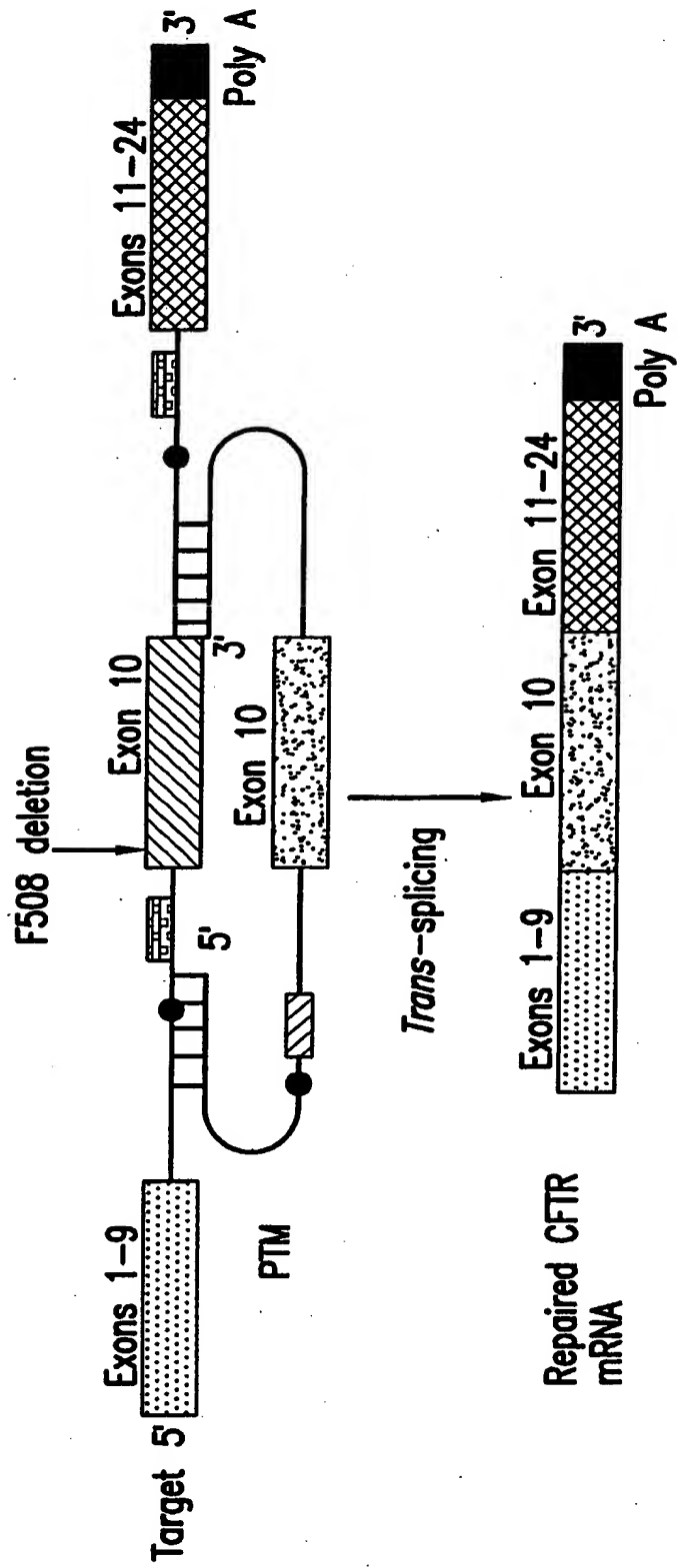


FIG.17

DOUBLE TRANS-SPLICING SPECIFIC TARGET

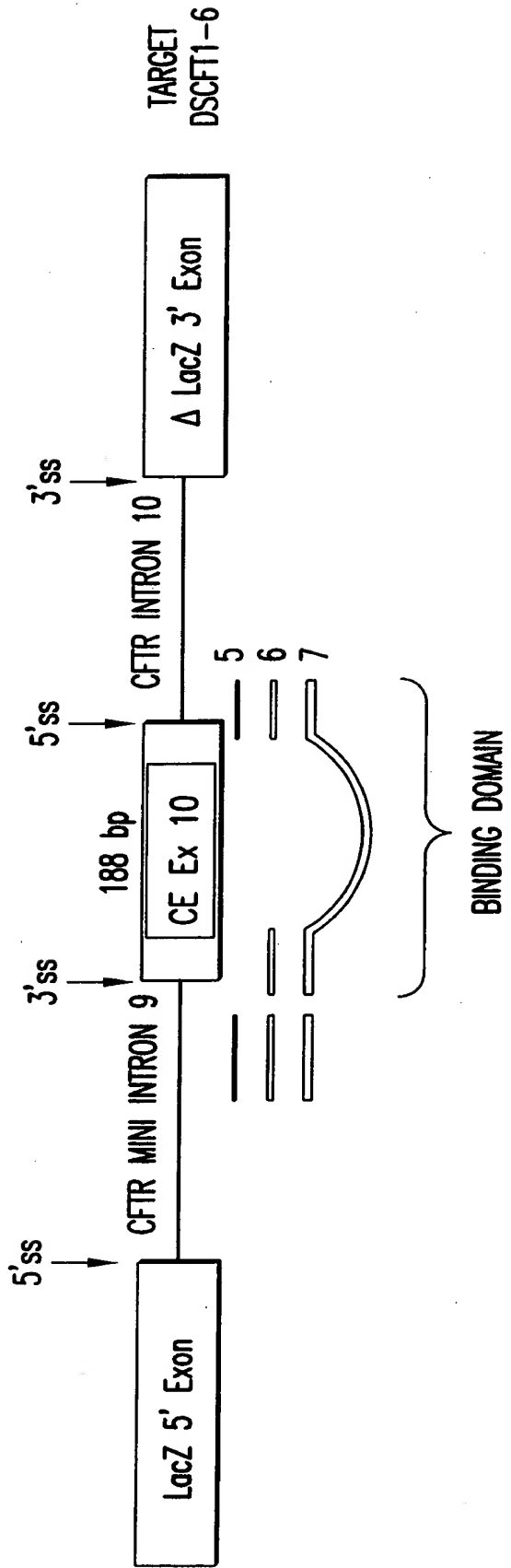


FIG.18



DOUBLE TRANS-SPLICING PTMS

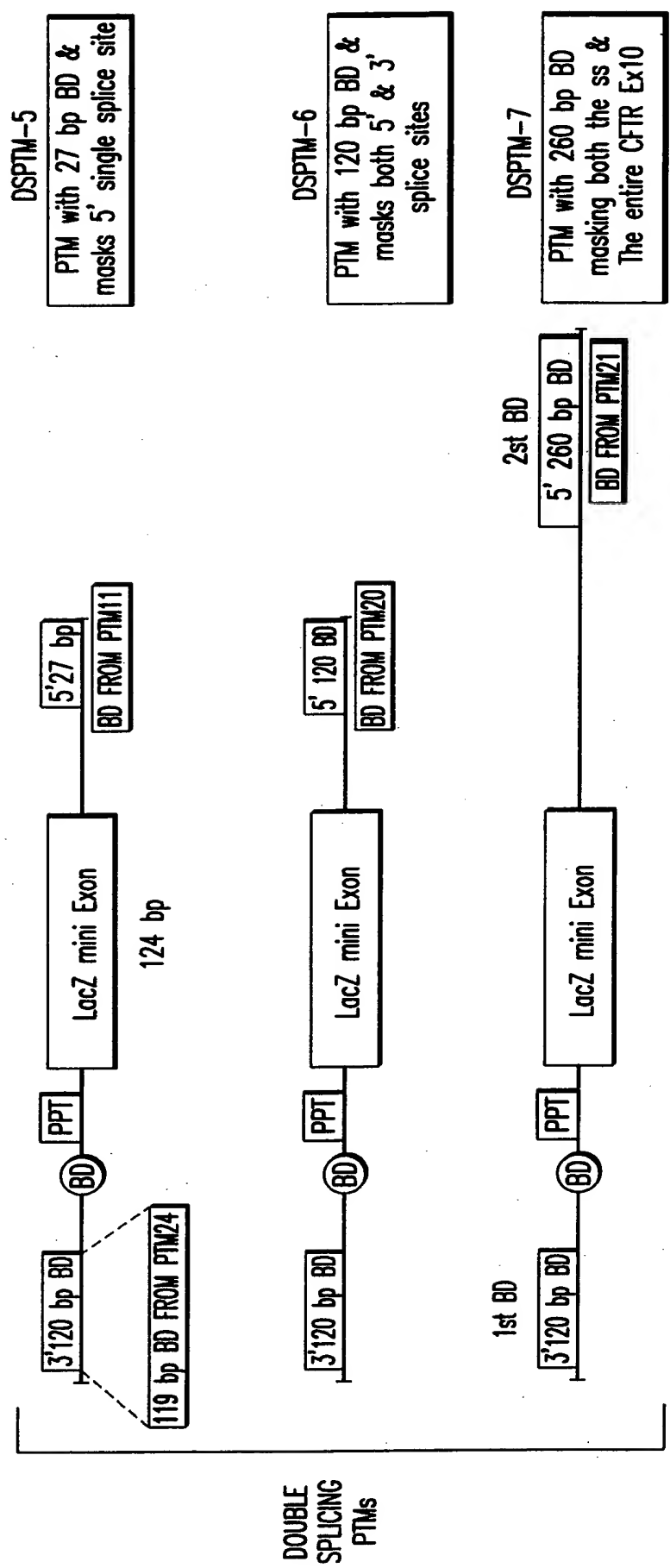
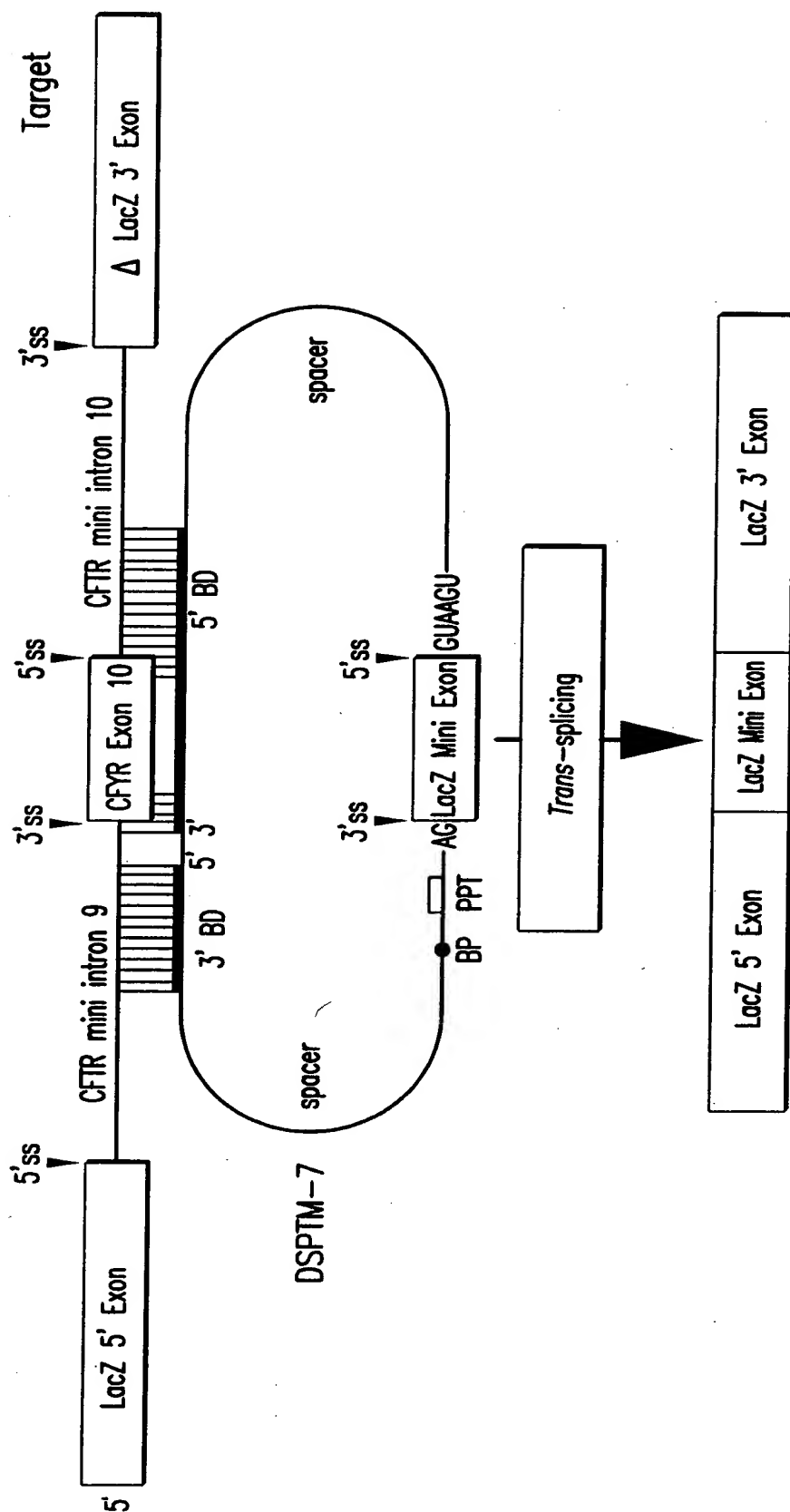


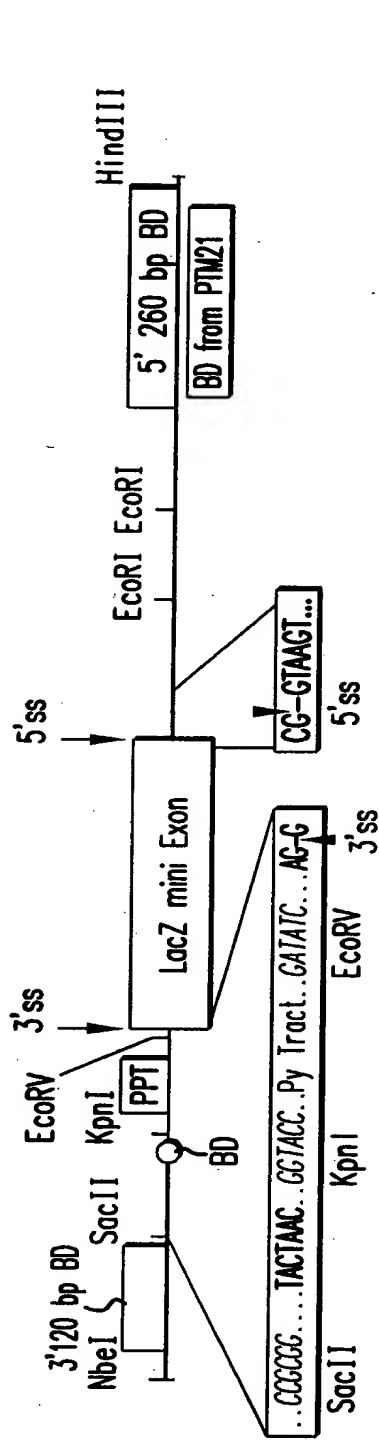
FIG.19

DOUBLE TRANS-SPLICING β -GAL MODEL



Repaired LacZ mRNA

FIG.20



(1) 3' BD (120 BP): GATTCACCTTGCCTCAATTATCATCCTAAGCAGAGTGATATCTTATTTGTAAGATTCTTAATTAACATTCATTGATTTC
AAATATTTAAATACTCCGTTTCATACACTCTGCTATGCAC

(2) Spacer sequences (24 bp): AACATTATTATAACCTTGTTCGAA

(3) Branch point, pyrimidine tract and acceptor splice site: TACTAAC TGGTACC TCTCTCTTTTTTTTTT GATAATCCTGCAG GGC GGC
BP Kpn I PPT EcoRV
3'ss LacZ mini exon

LacZ mini 5'ss
exon

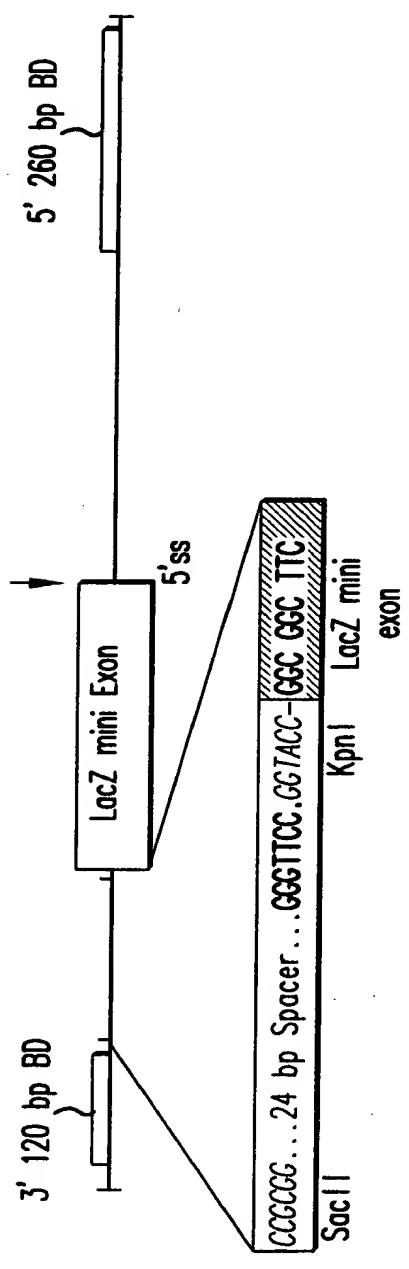
(4) 5' donor site and 2nd spacer sequence: TGA ACG GTAAGT GTTATCACCGATATGTCCTAACCTGATTCGGCCCTTCGATACG

CTAAGATCCACCGG

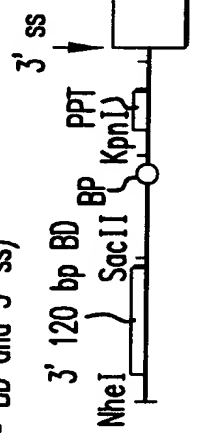
(5) 5' BD (260 BP): TCAAAAGTTTCACATAATTTCTTACCCTTCTTGAATTCATGCTTTGATGACGCTTCTGTATCTATATCATTCGAA
ACACCAATCATTTTCTTTAATGCTGCCCTGGCATAATCTCGGAAACATGATAACACAAIGAAATCTTCCACTGCTTAA
AAAACCCCTCGAAATCTCCCAATTTCTCCCAATATCATCATTACAACCTGAACCTCGGAAATAAAACCCATCATTTAACTCA
TTATCAAAATCACCG

FIG.21

DSPTM8: (Δ 3' ss: 3' splice elements i.e. BP, PPT & AG dinucleotide has been deleted and replaced with random sequences, but still has the functional 5' splice site)



PTM29 (lacks 2nd BD and 5' ss)



PTM30 (lacks 1st BD and 3' ss)

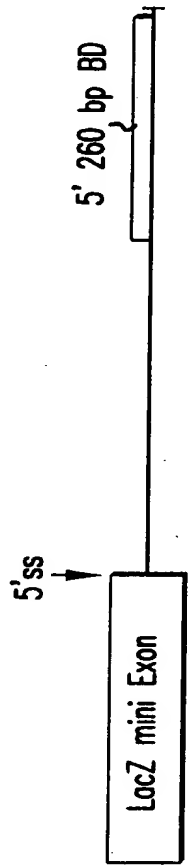


FIG.22

Mutants

ACCURACY OF DOUBLE TRANS-SPICING REACTION

Splice Junction 2

LacZ 5' Exon

10
T T T A T C C C C G T T T A C A G

20

G G C G G C T T C G T C T G G G A C T G G G T G G A T C A G T C C C T G A T T A A A T A T G A T G A A A A

30

40

50

60

70

LacZ Mini Exon

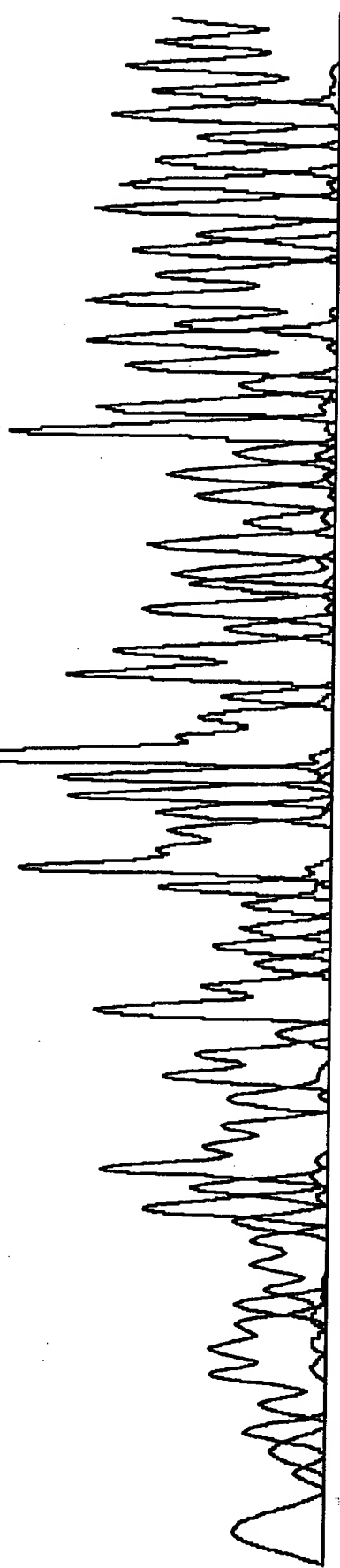


FIG.23A

ACCURACY OF DOUBLE TRANS-SPlicing REACTION

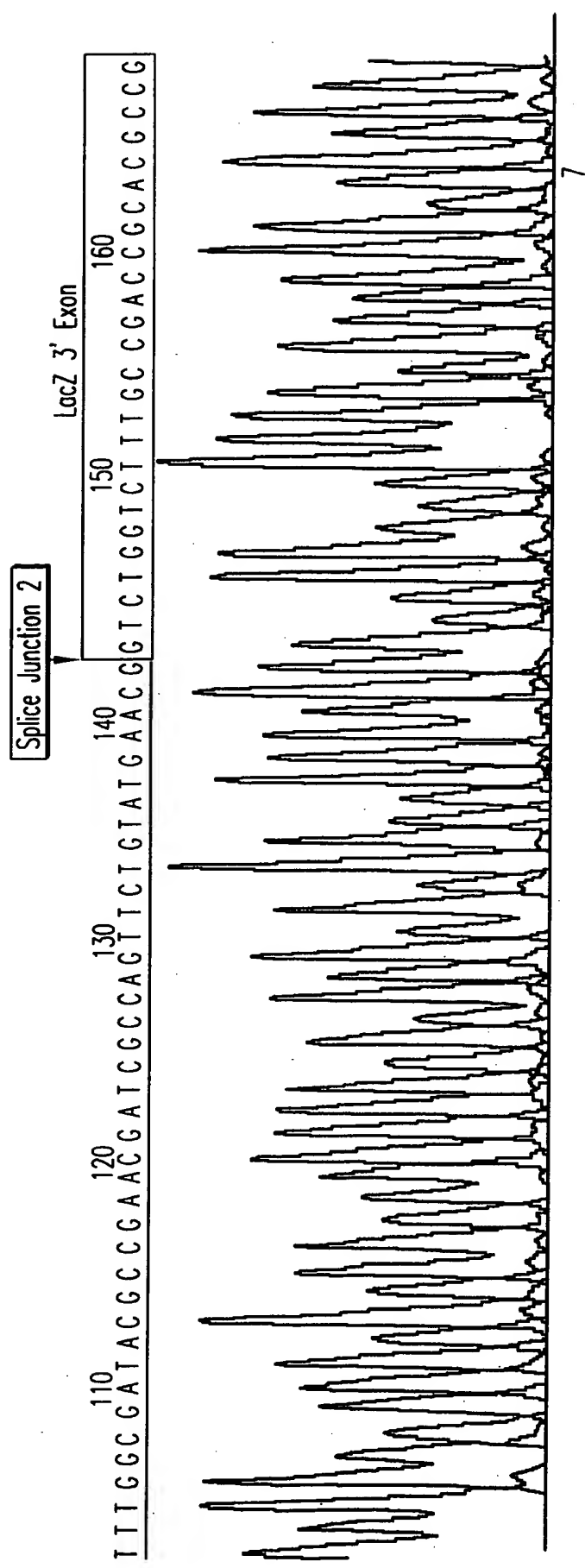


FIG.23B

Double *Trans*-splicing Produces Full-length Protein

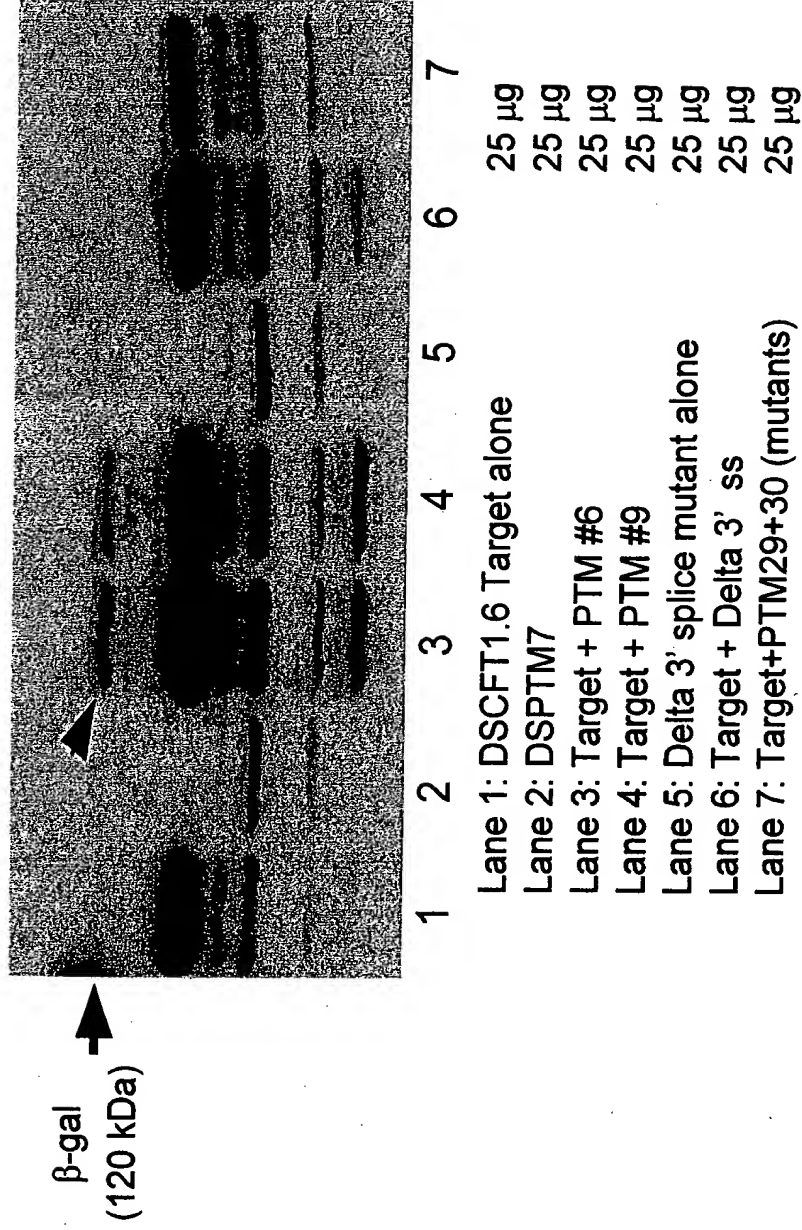
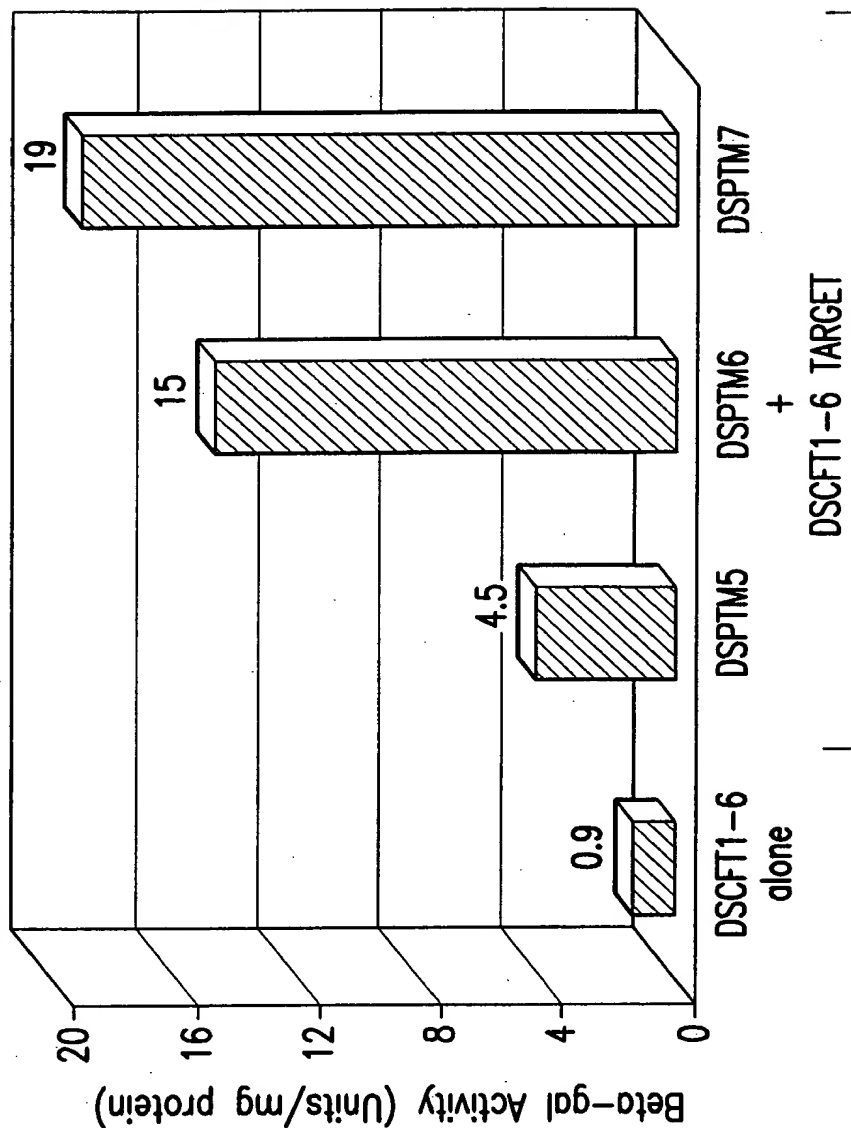


FIG.24



RESTORATION OF β -GAL FUNCTION BY DOUBLE TRANS-SPICING



Beta-gal Activity above
the Background level

DSPTM5: 5 fold
DSPTM6: 17 fold
DSPTM7: 21 fold

FIG.25

RESTORATION OF β -GAL ACTIVITY IS DUE TO DOUBLE RNA TRANS-SPLICING EVENTS

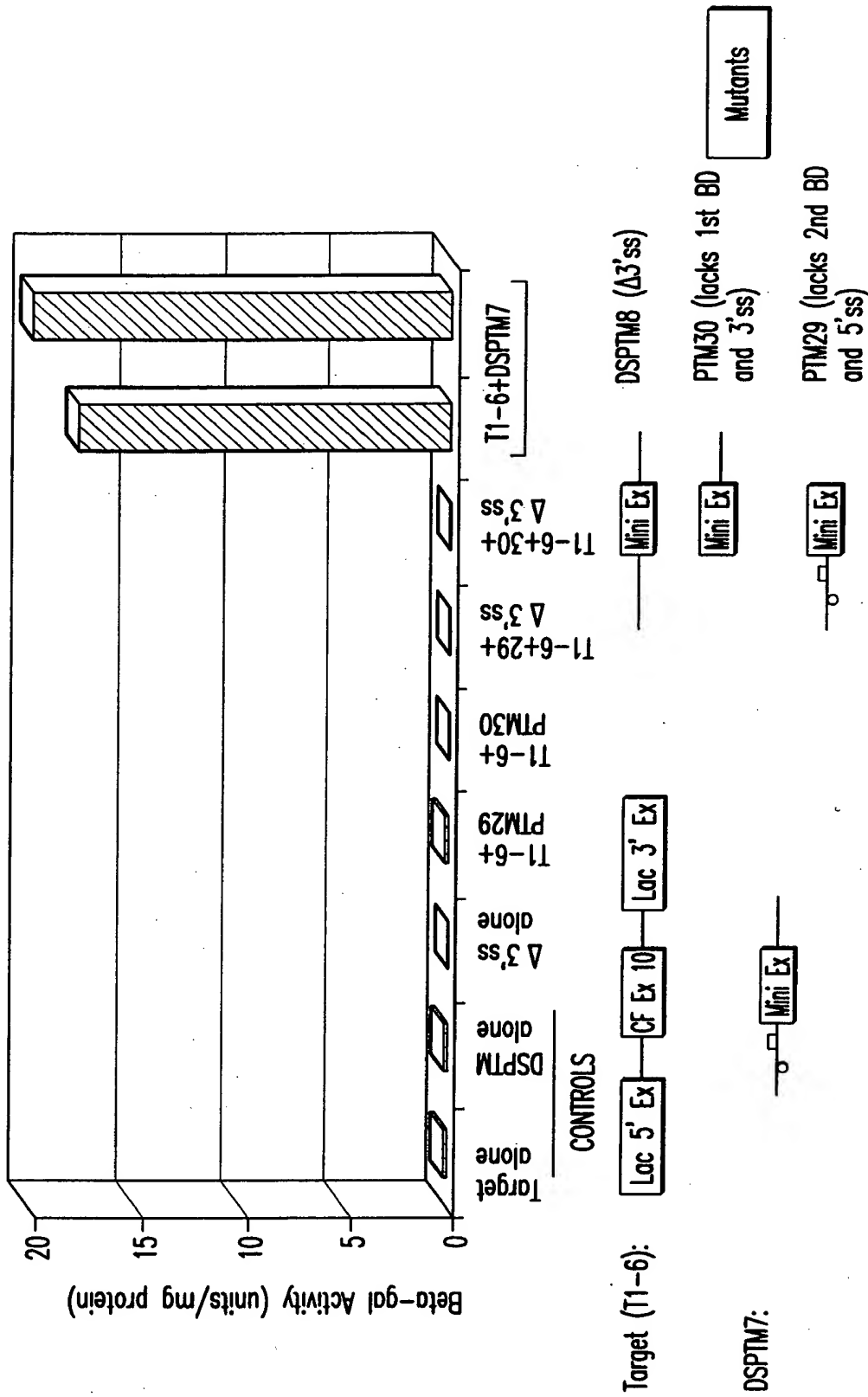
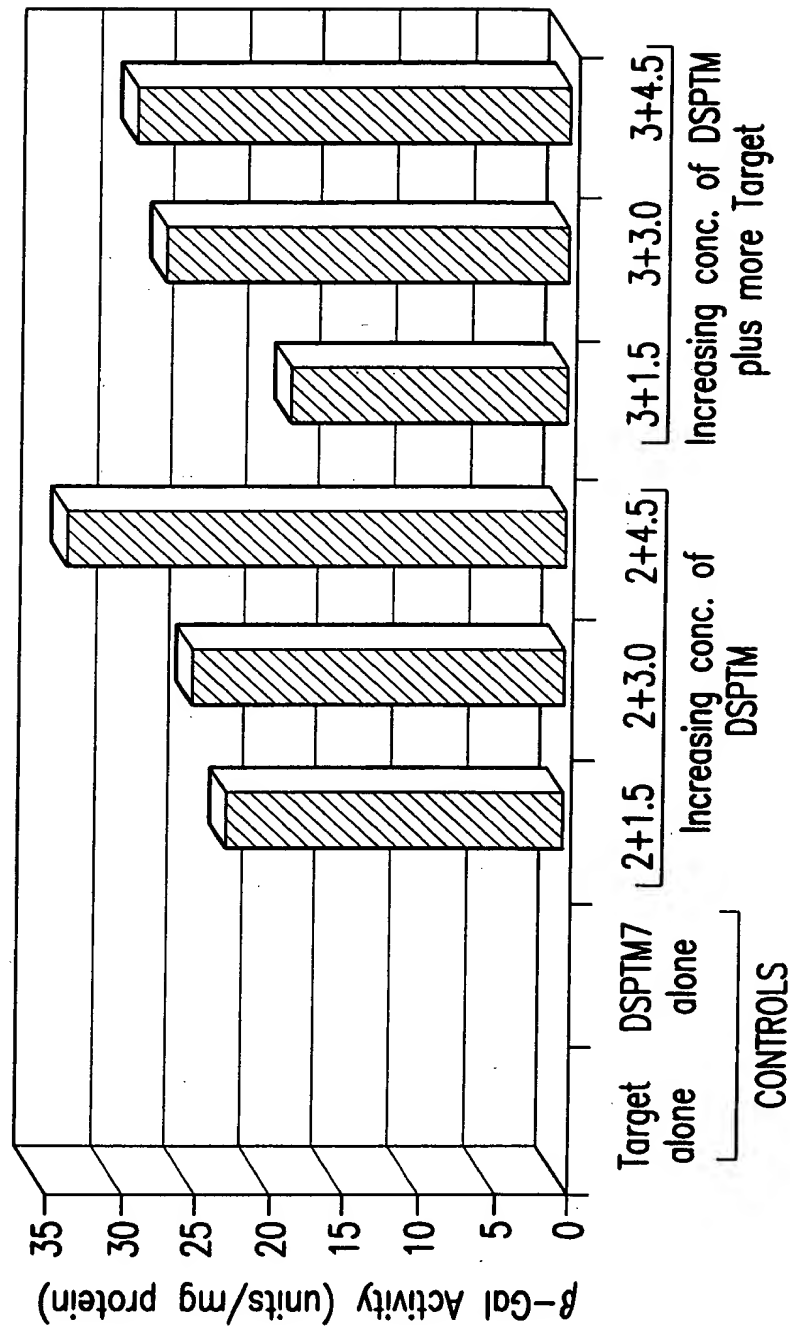


FIG.26



DOUBLE TRANS-SPLICING: TITRATION OF TARGET & PTM



The current level of beta-gal activity due to double trans-splicing is ~ 1-1.5% of the best single splice model (3' exon replacement)

FIG.27

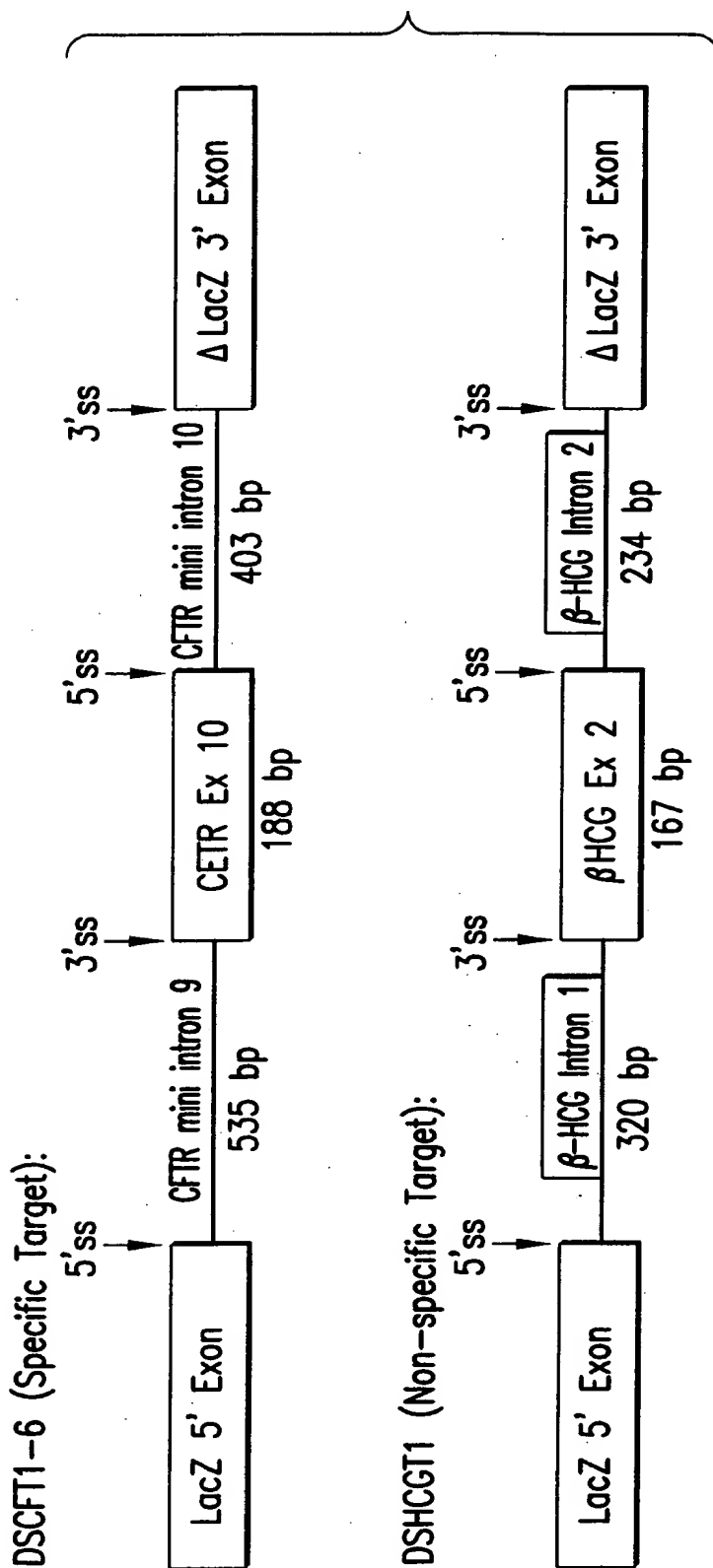


FIG.28



SPECIFICITY OF DOUBLE *TRANS*-SPLICING REACTION

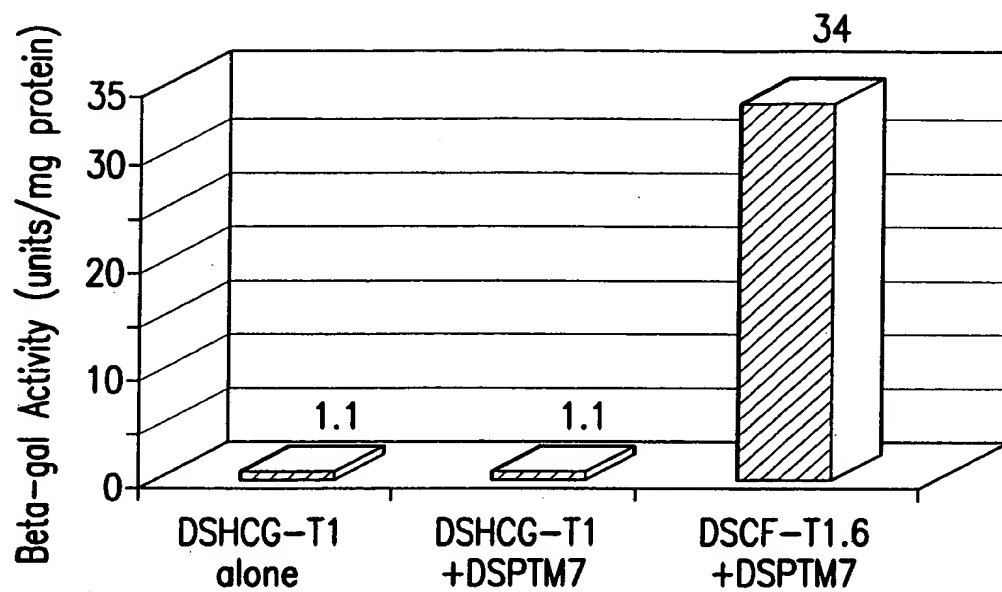


FIG.29

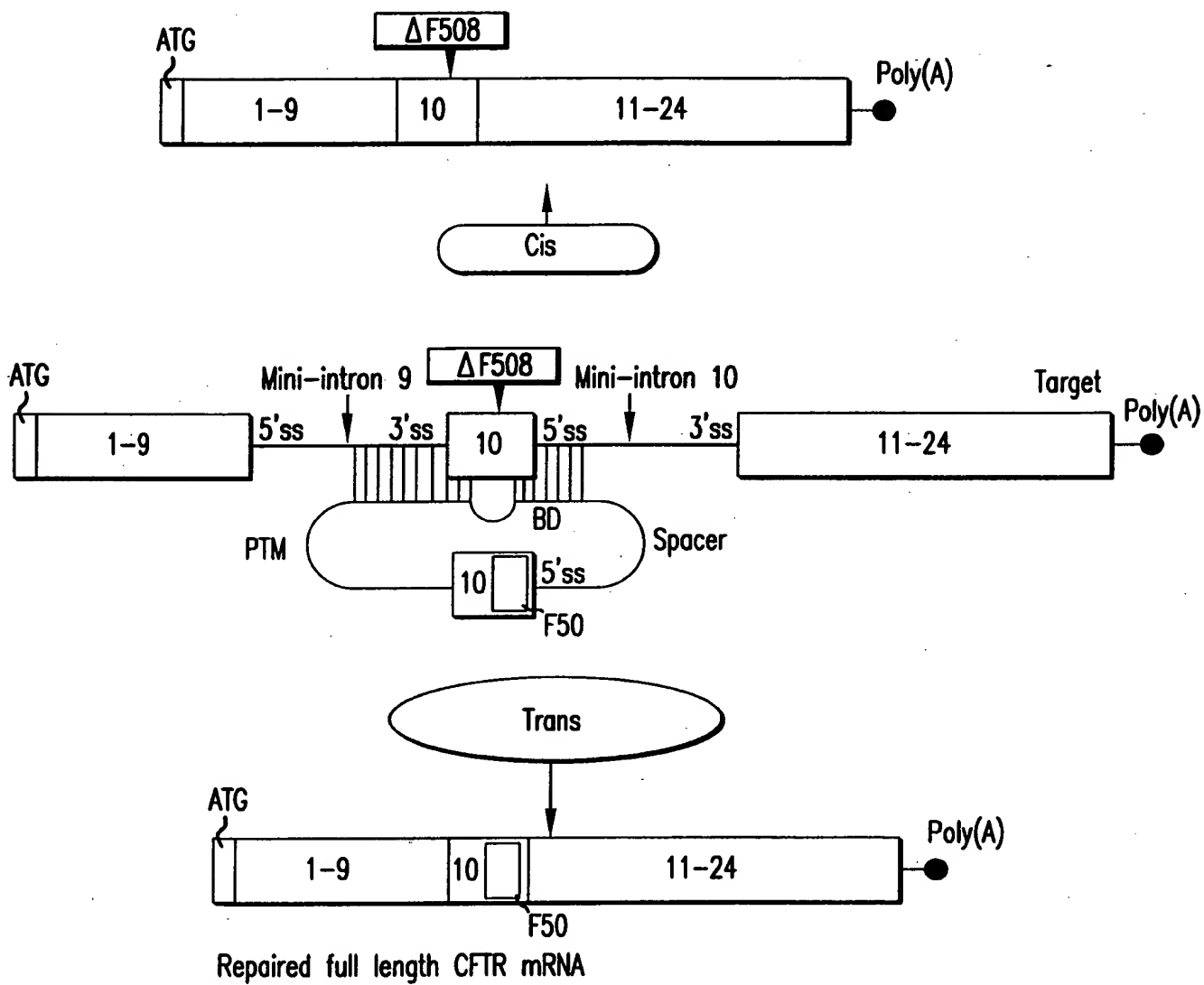
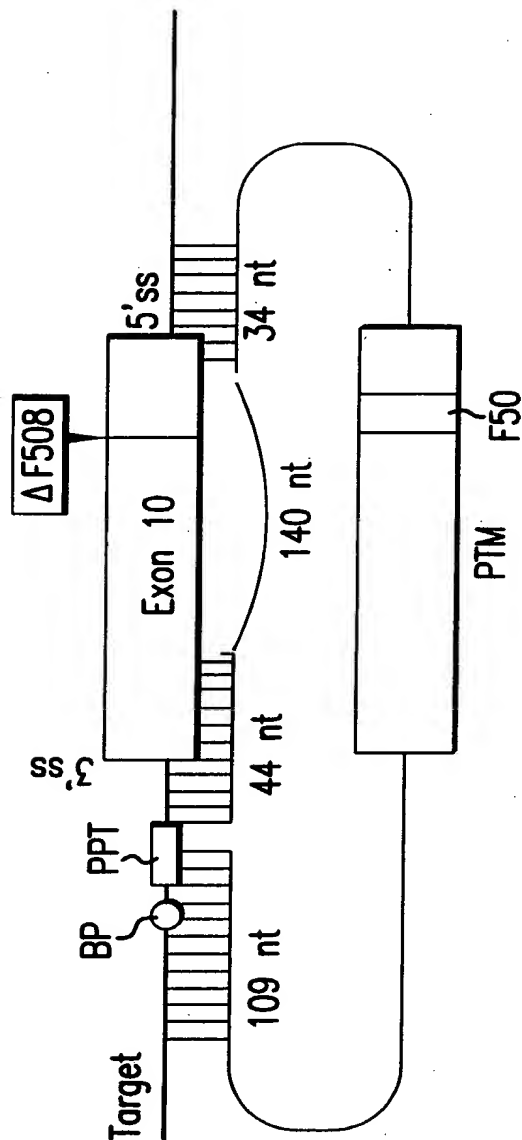


FIG.30

PTM with a long binding domain masking
two splice sites and part of exon 10
in a mini-gene target

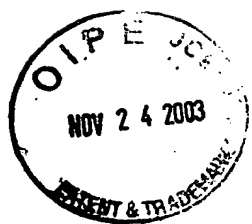


ACGAGCTTGCTCATGATGATCGGCCGAGTTAGAACCAAGTGAAGGCAAGATCAAAACATTCGCG
GCCGCATCAGCTTTTCAGAGCCAAITCAGTTCGATCATGCCCGGTACCATCAAGGAGAAATAT
CTTCGGCGTCAGTACGAGGAGTACCGCTATCGCTCGGTGATTAAGGCCGTGTCAGTTGGAGGAG

MCU in exon 10 of PTM

88 OF 192 (46%) bases in PTM exon 10 are not complementary to
its binding domain (bold and underlined).

FIG.31



Sequence of a double
Trans-spliced product

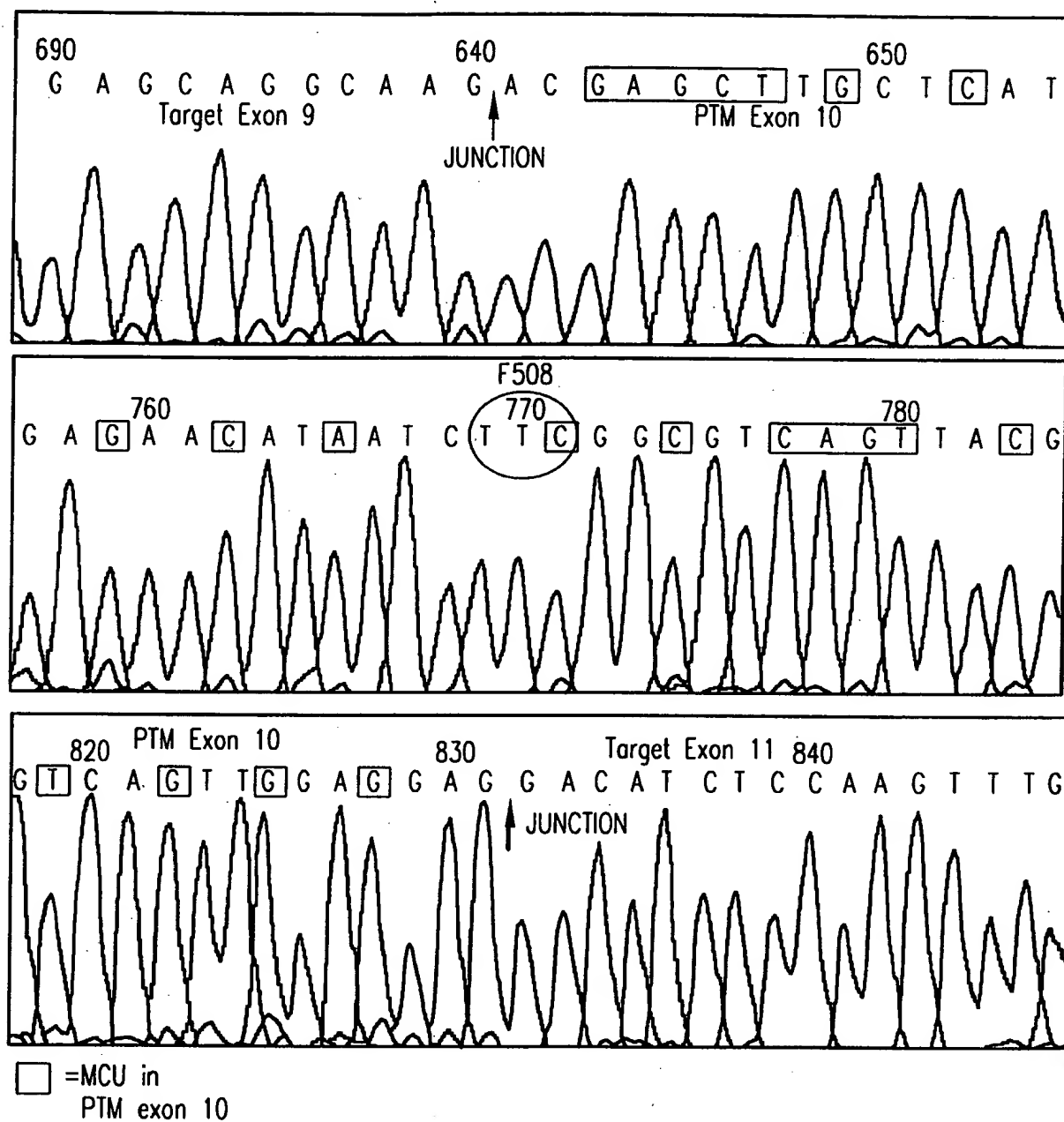


FIG.32

CF-TR Repair: 5' Exon-Replacement schematic
diagram of a PTM binding to the splices site
of intron 10 of a mini-gene target

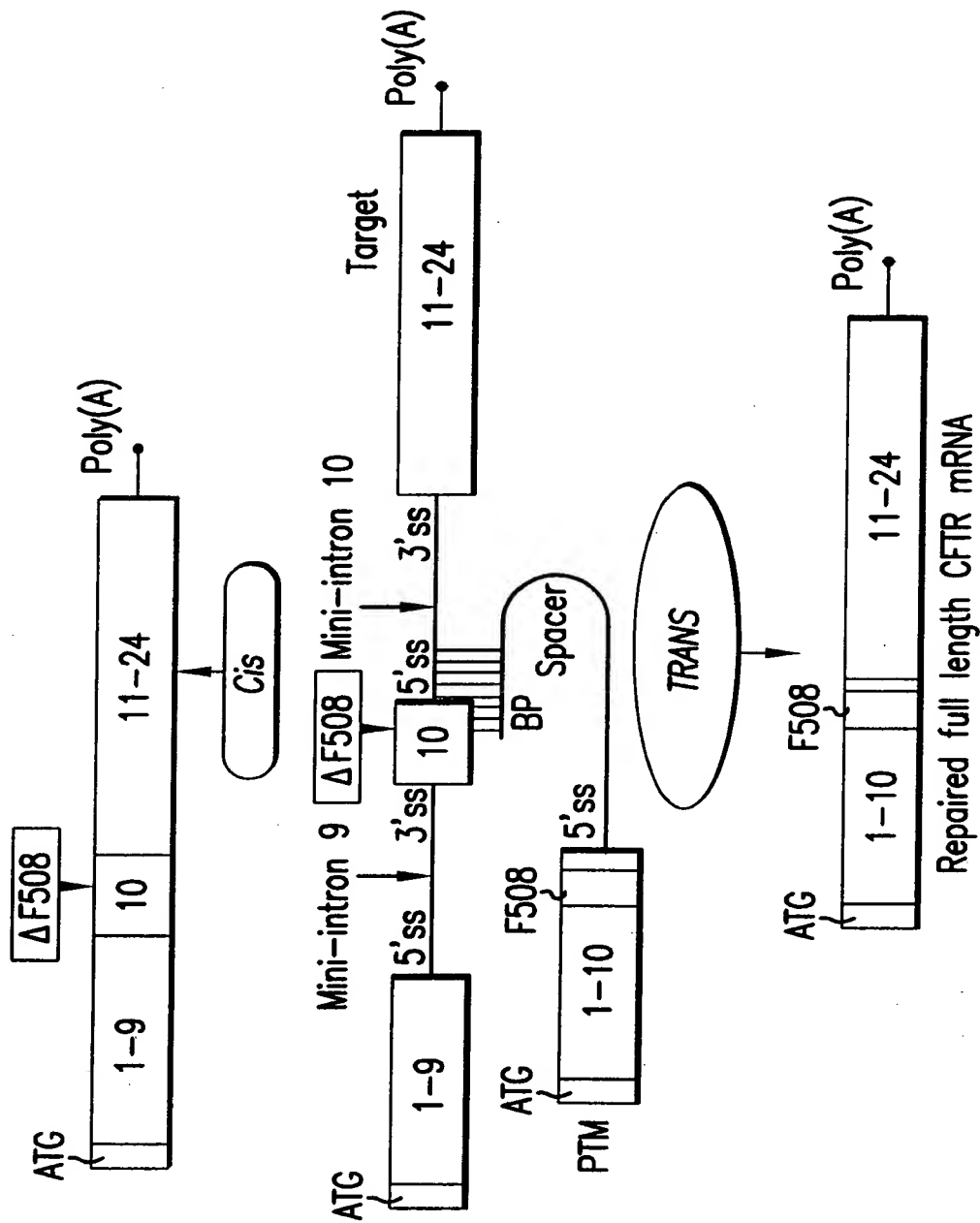


FIG.33



PTM with a short binding domain masking a single splice site in a mini-gene target.

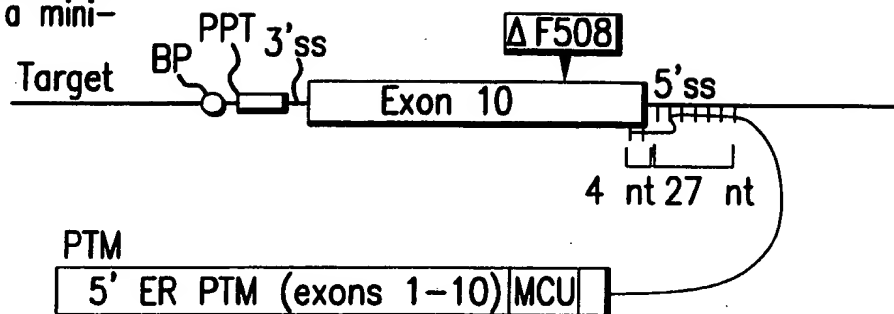


FIG.34A

PTM with a long binding domain masking two splice sites in a mini-gene target.

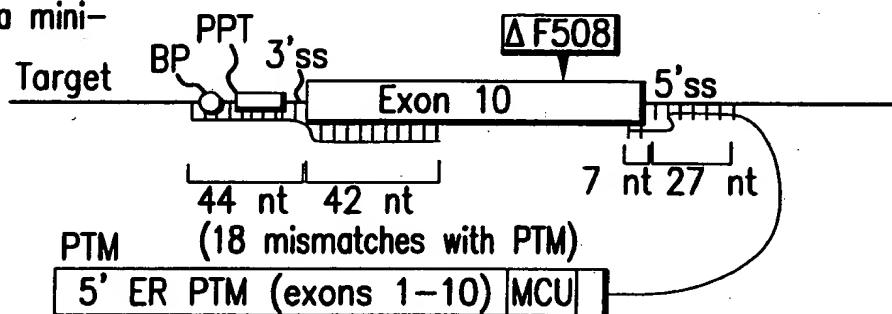


FIG.34B

PTM with a long binding domain masking two splice sites and the whole of exon 10 in a mini-gene target.

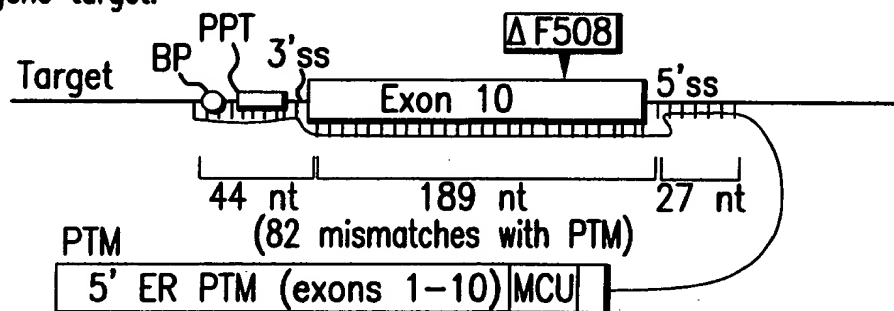
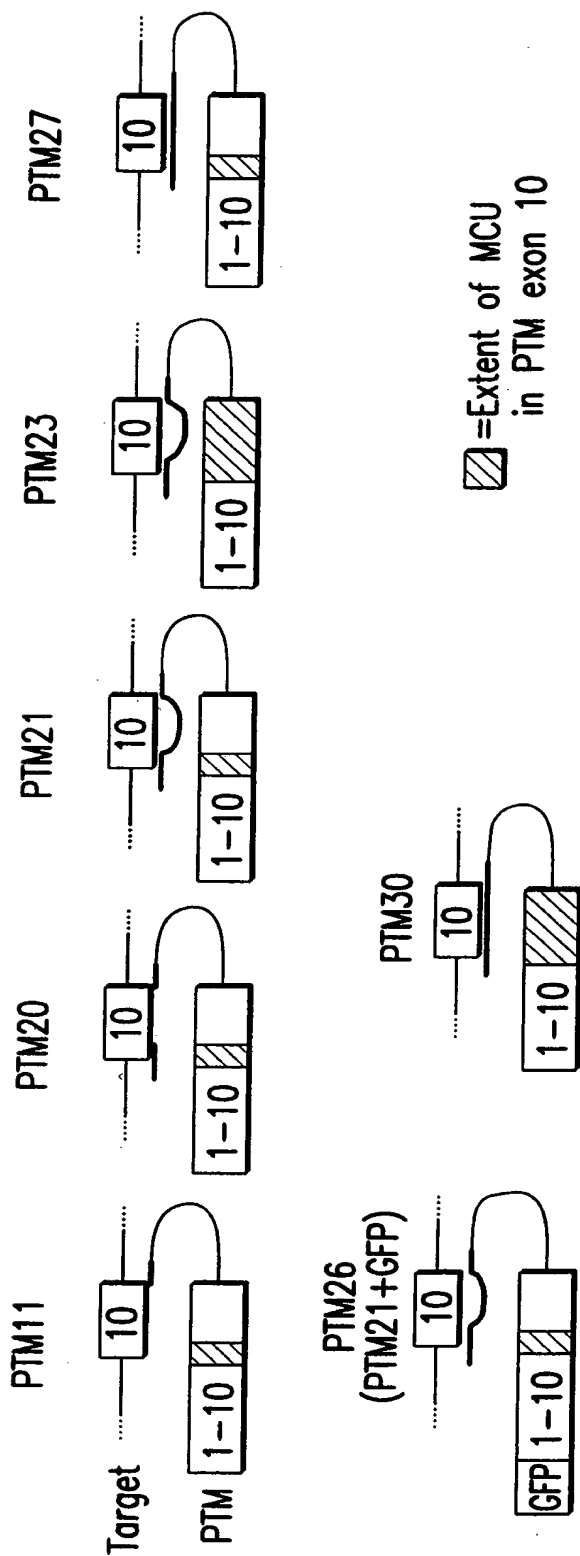


FIG.34C



MCU in exon 10 of PTM
88 of 192 (46%) bases in PTM exon 10 are not complementary to its binding domain.

ACGAGCTTGCCTCATGATGATCGCGGAGTTAGAACCAAGTGAAGGCAAGATCAAAACATTCCG
GCCGCATCAGCITTTGCAGCCAAITCAGTGGATGATGCCCGGTACCATCAAGGAGAAACATAAT
CTTCGGCGTCAGTACGACGAGTACCGCTATCCGTCGGTGAIAAGCCGTGTCAGTTGGAGGAG

FIG.35



FIG.36A



Cis-spliced product
[Primers CF1+CF111]

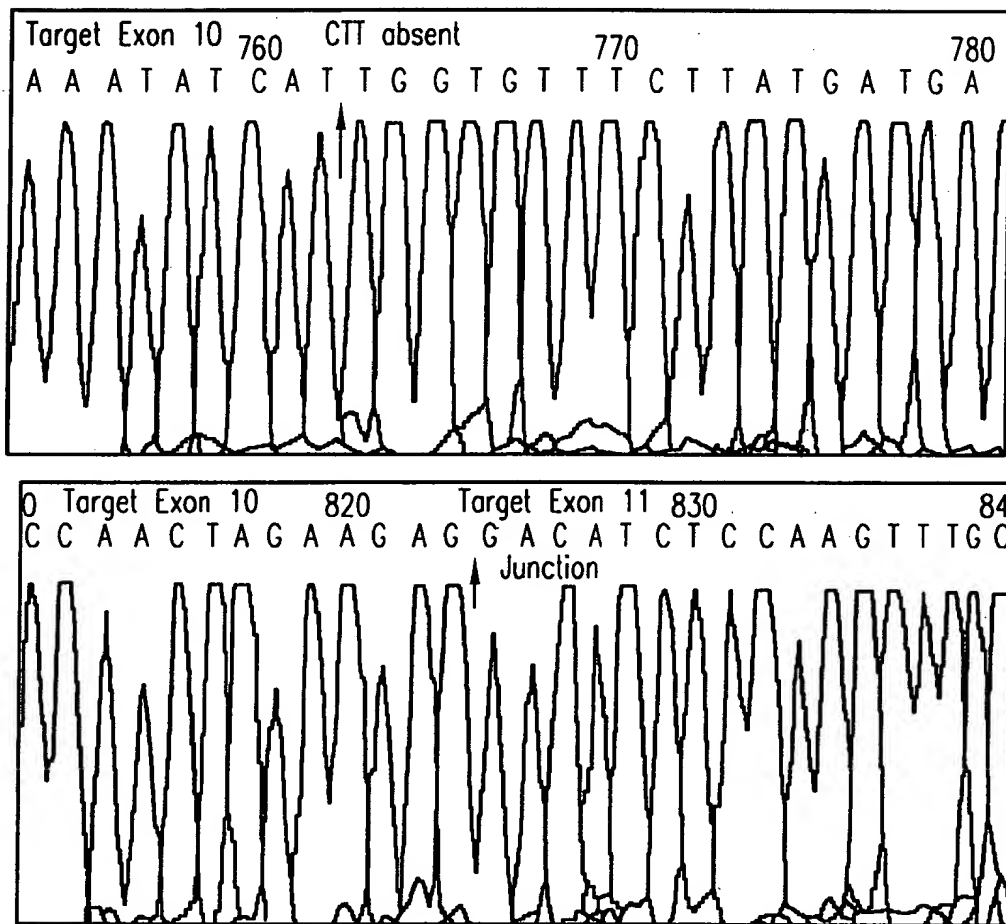


FIG.36A-1

Handwritten notes and signatures in the bottom right corner, including a date "11/24/03" and a signature.



Trans-spliced product
[Primers CF93+CF111]

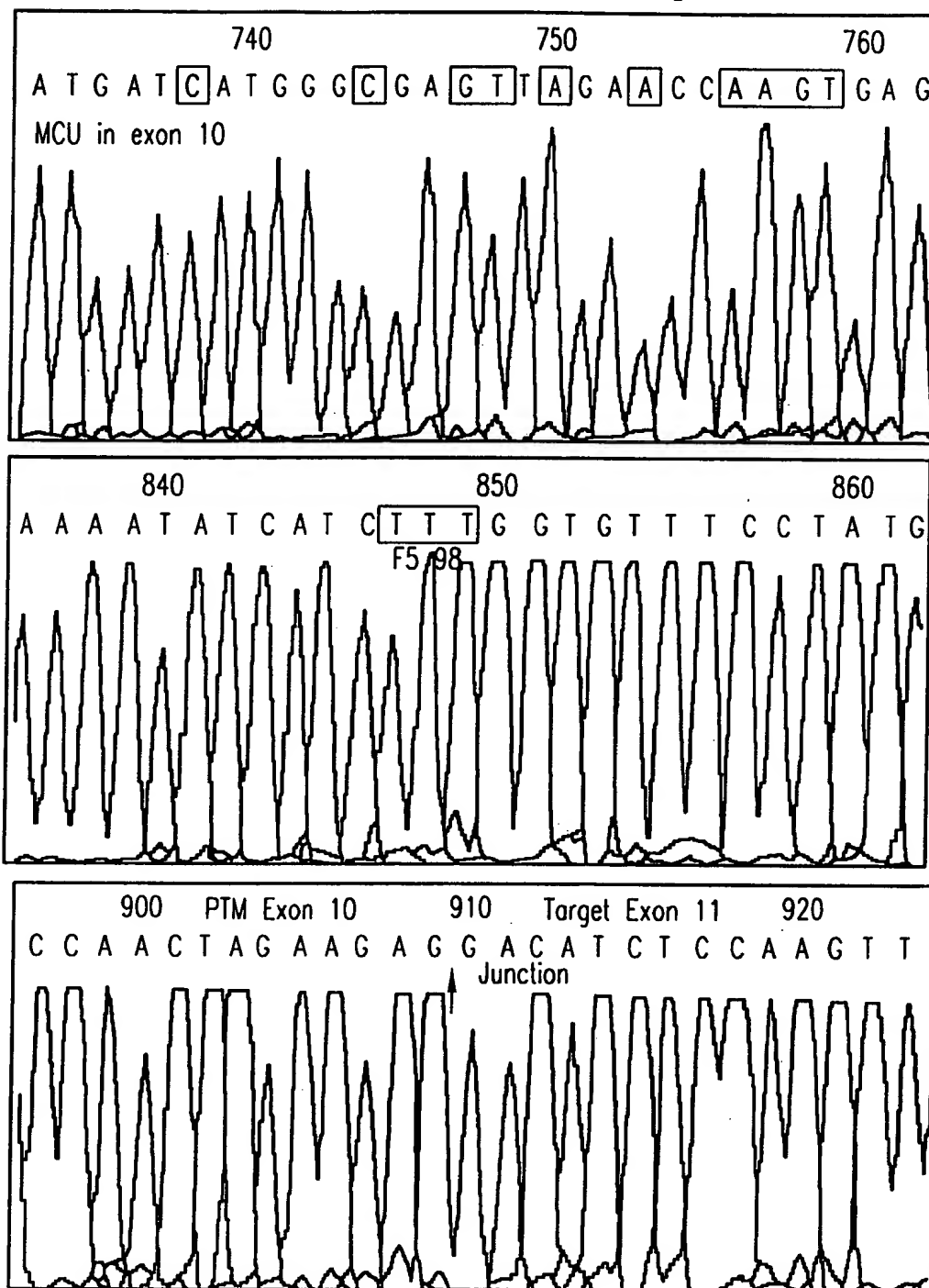


FIG.36B

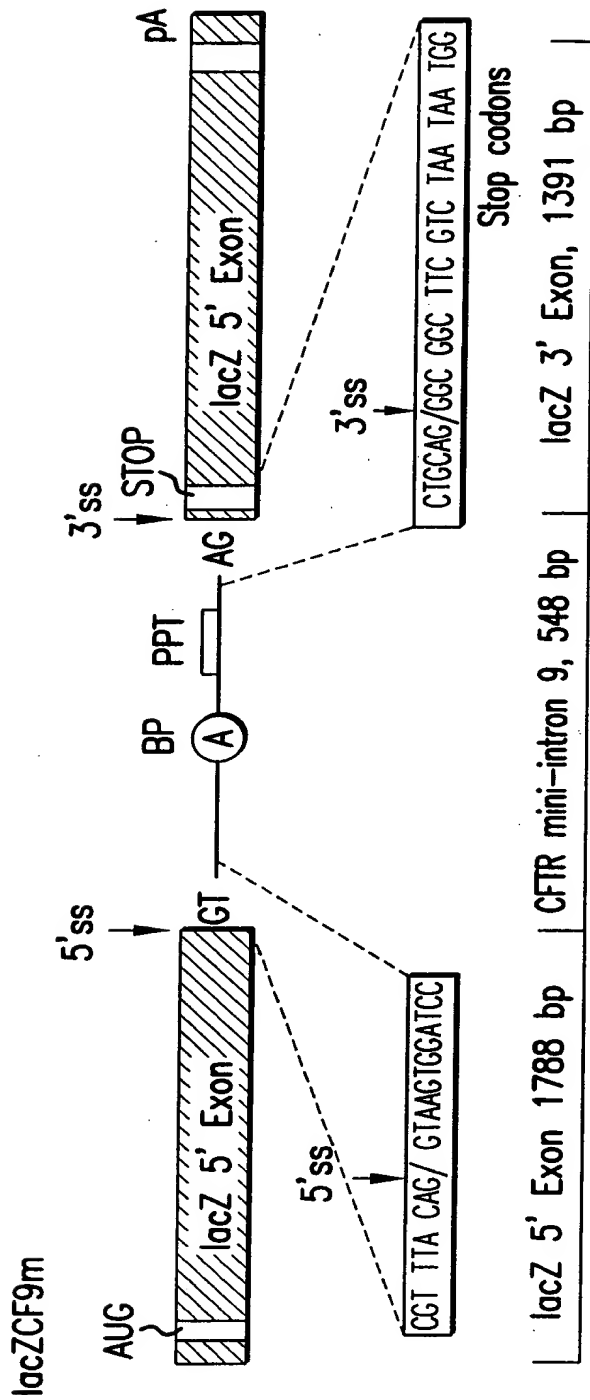


FIG.37A

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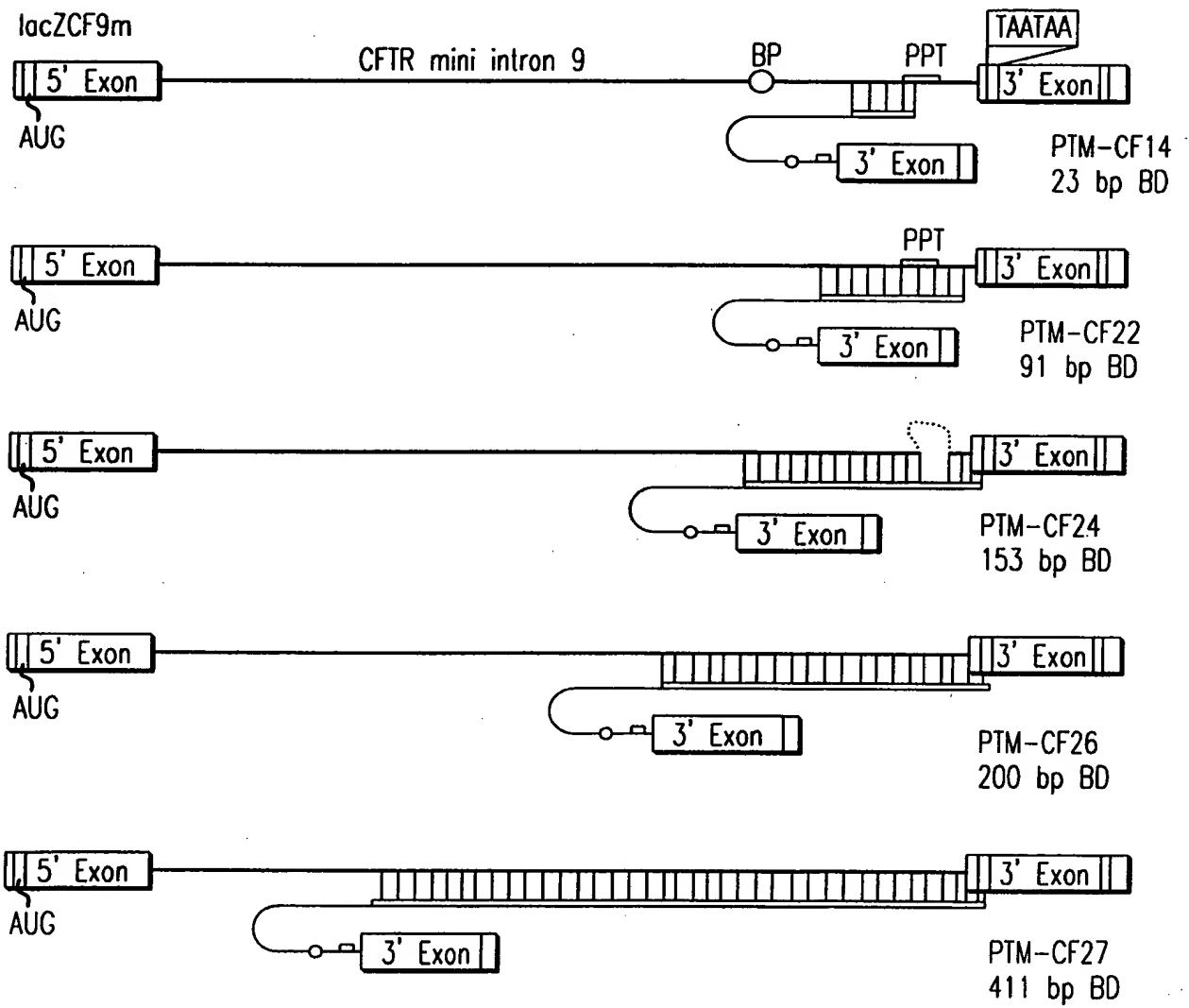
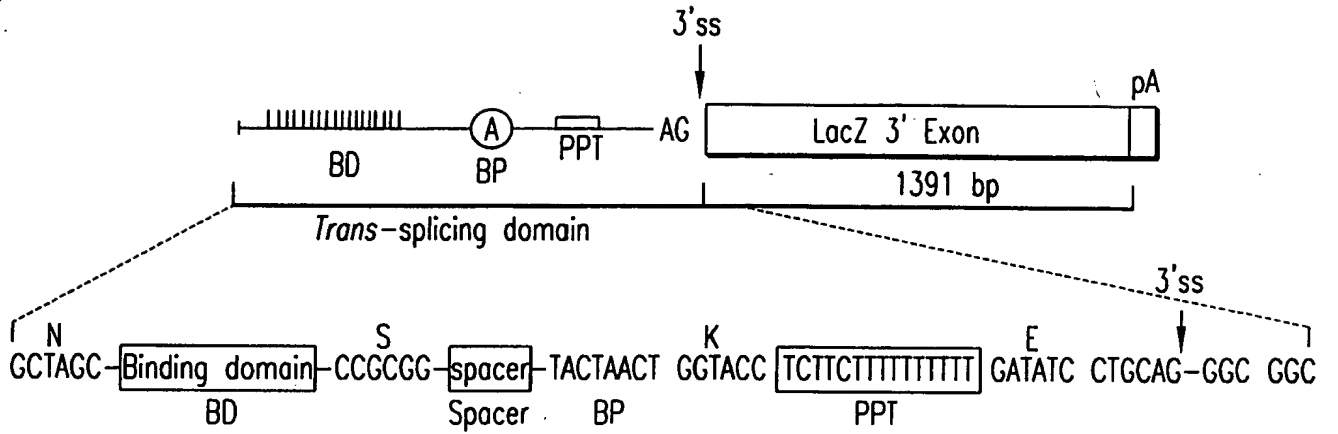


FIG.37B

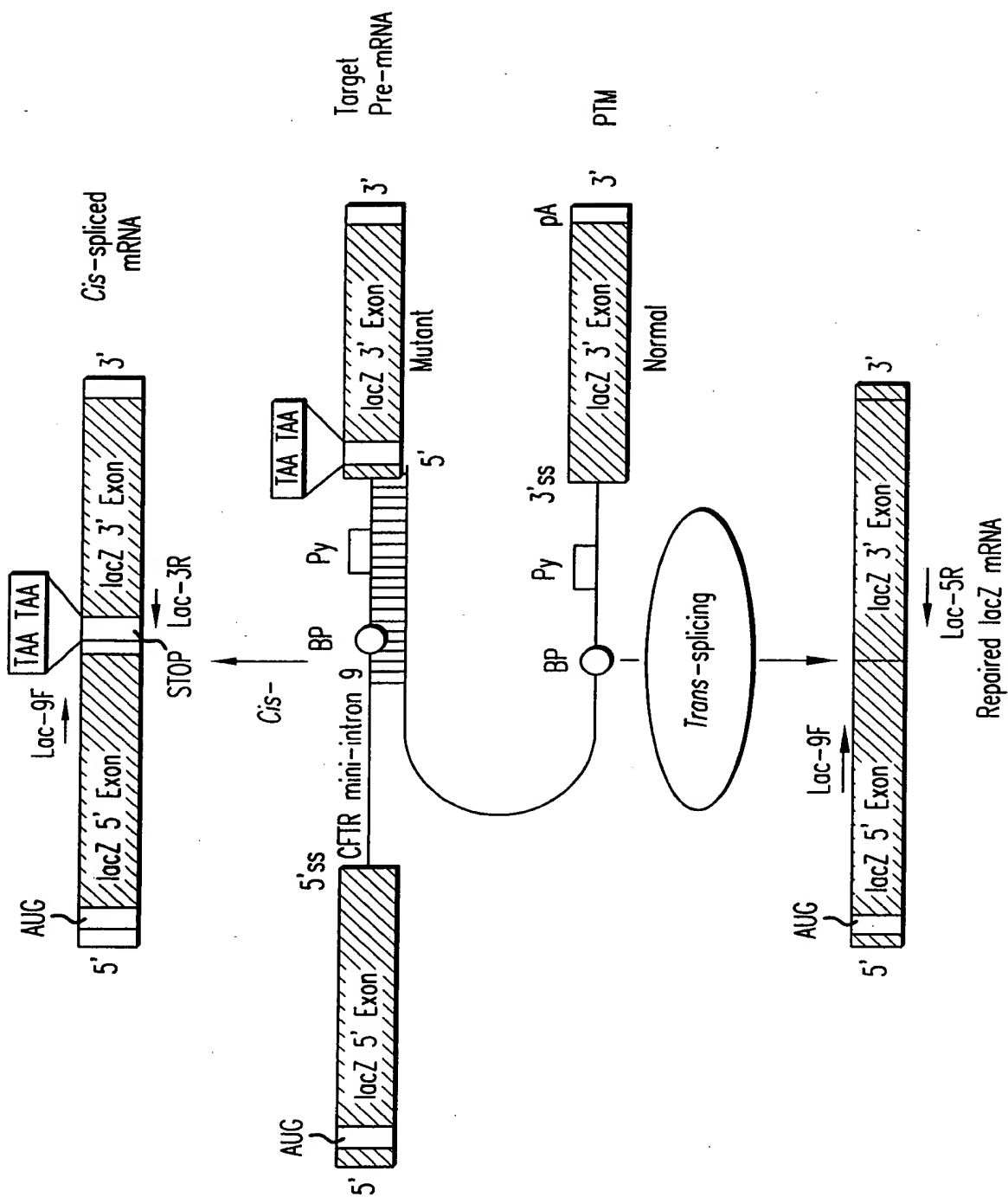
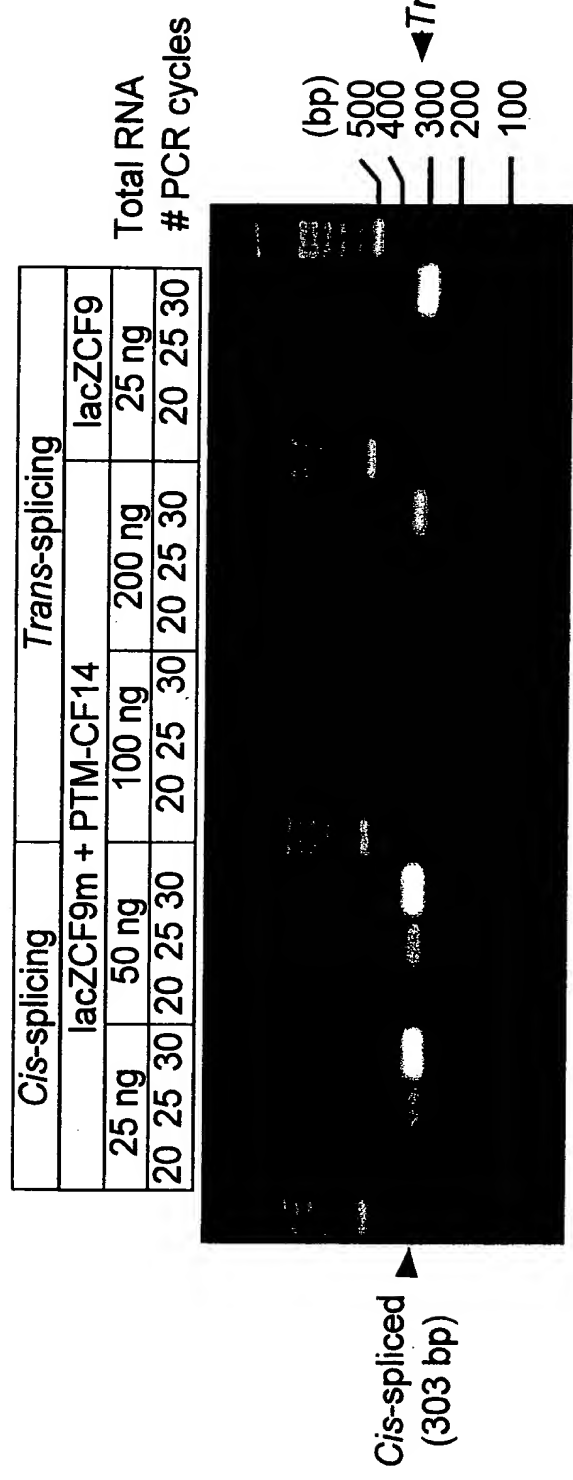
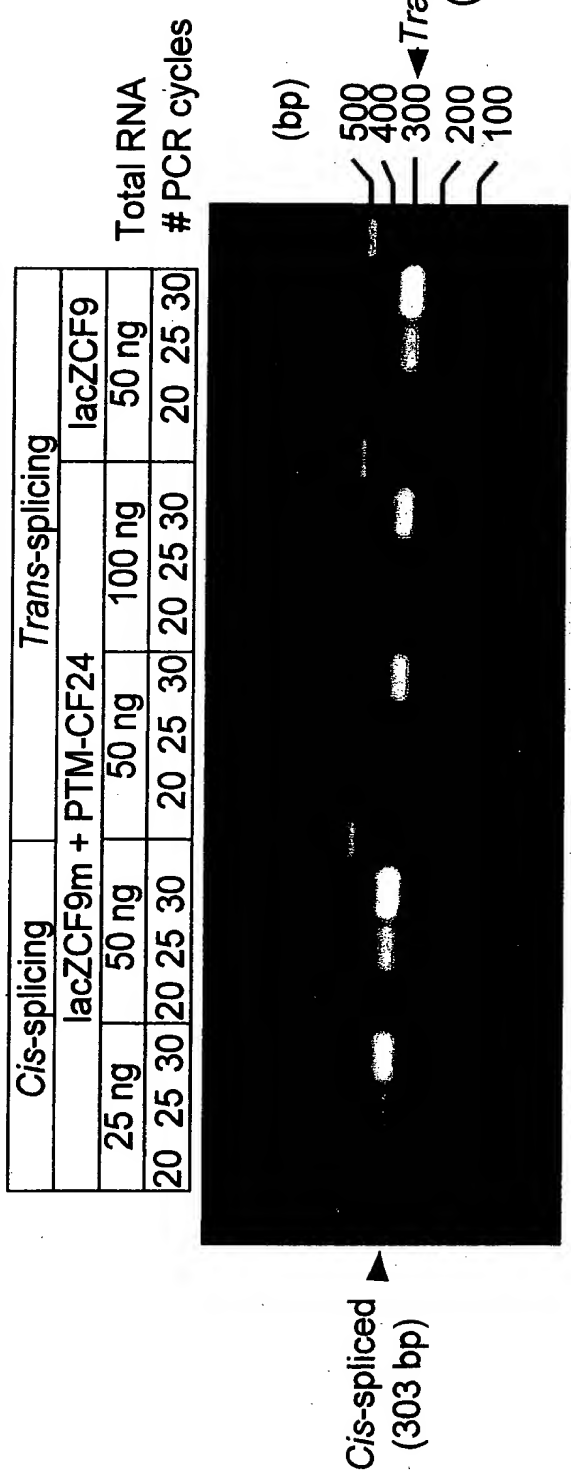


FIG.37C



1 2 3 4 5 6 M 7 8 9 10 11 12 M 13 14 15



1 2 3 4 5 6 M 7 8 9 10 11 12 M 13 14 15

FIG.38A

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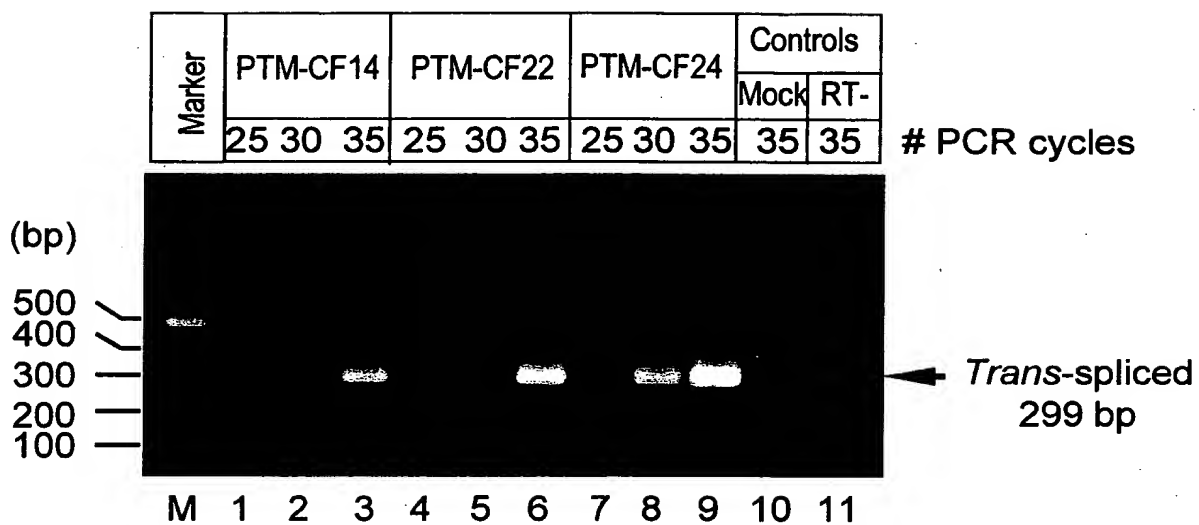


FIG.38B

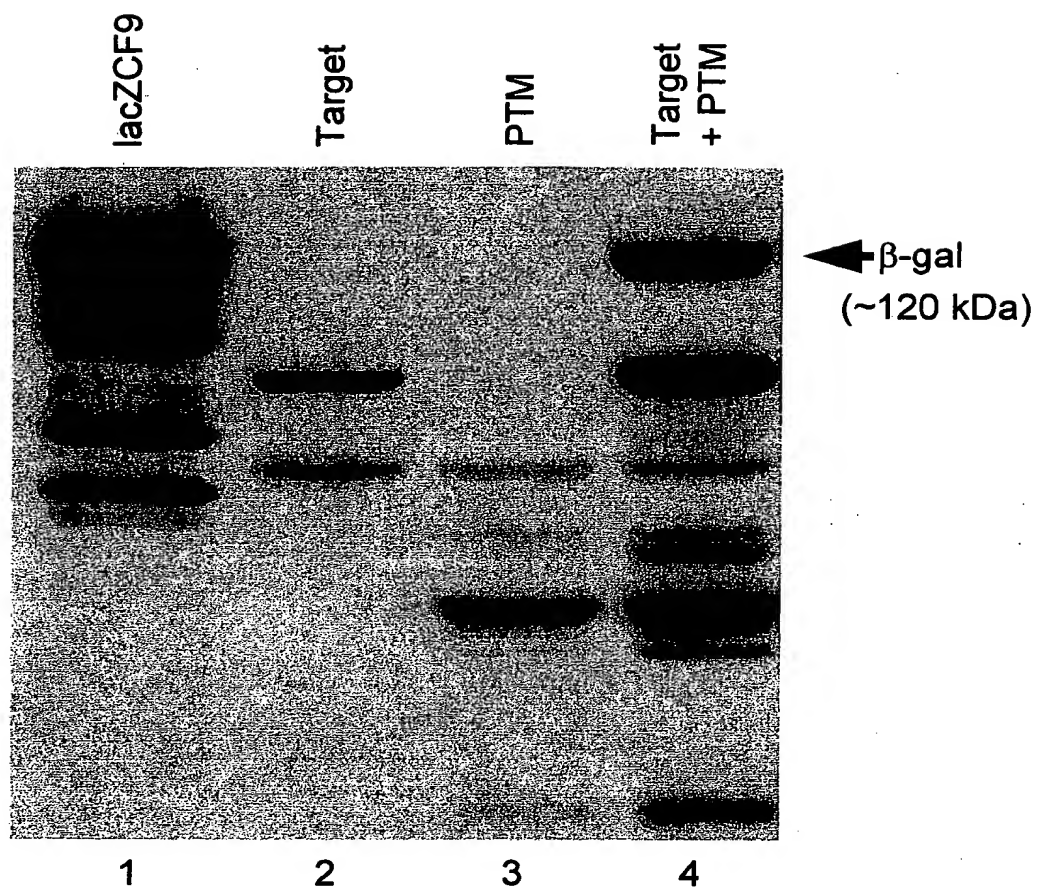


FIG.39

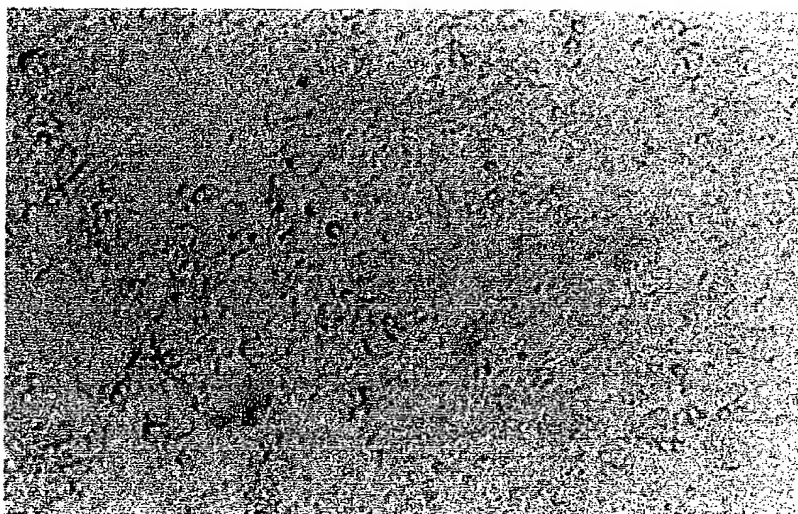


FIG.40A(a)

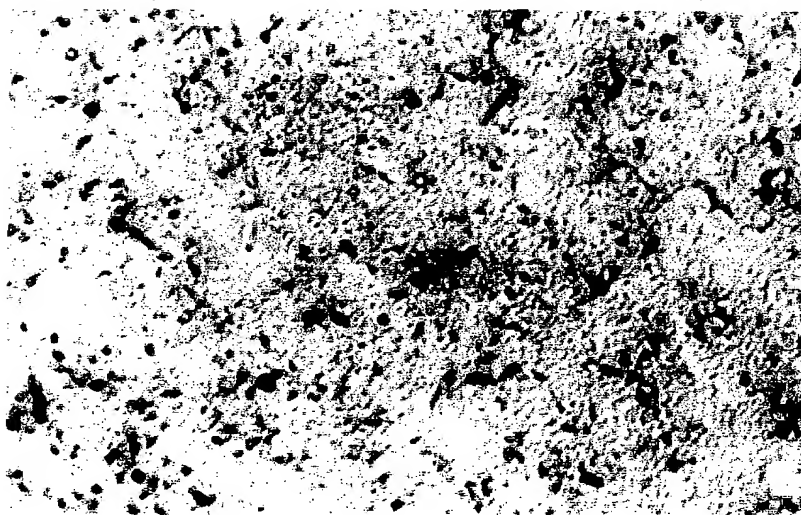


FIG.40A(b)

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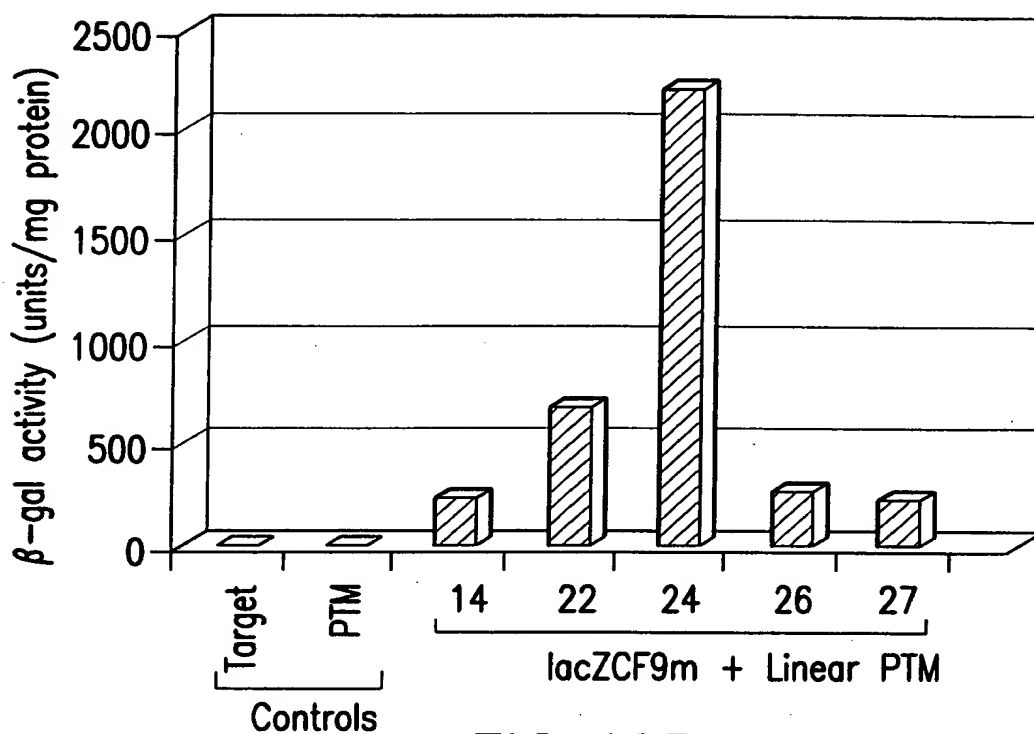
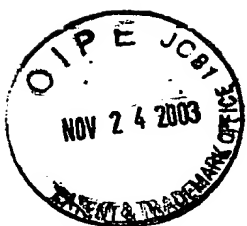


FIG.40B

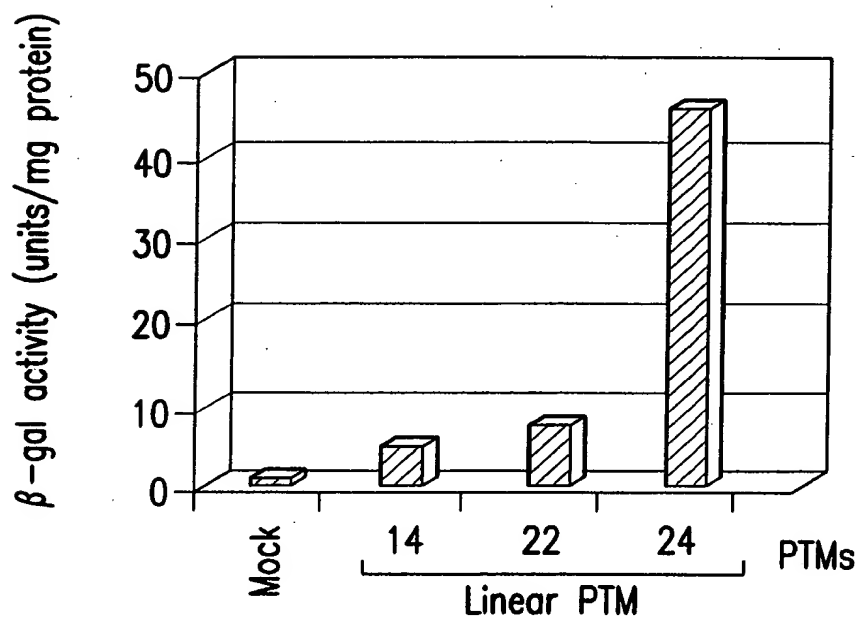


FIG.40C

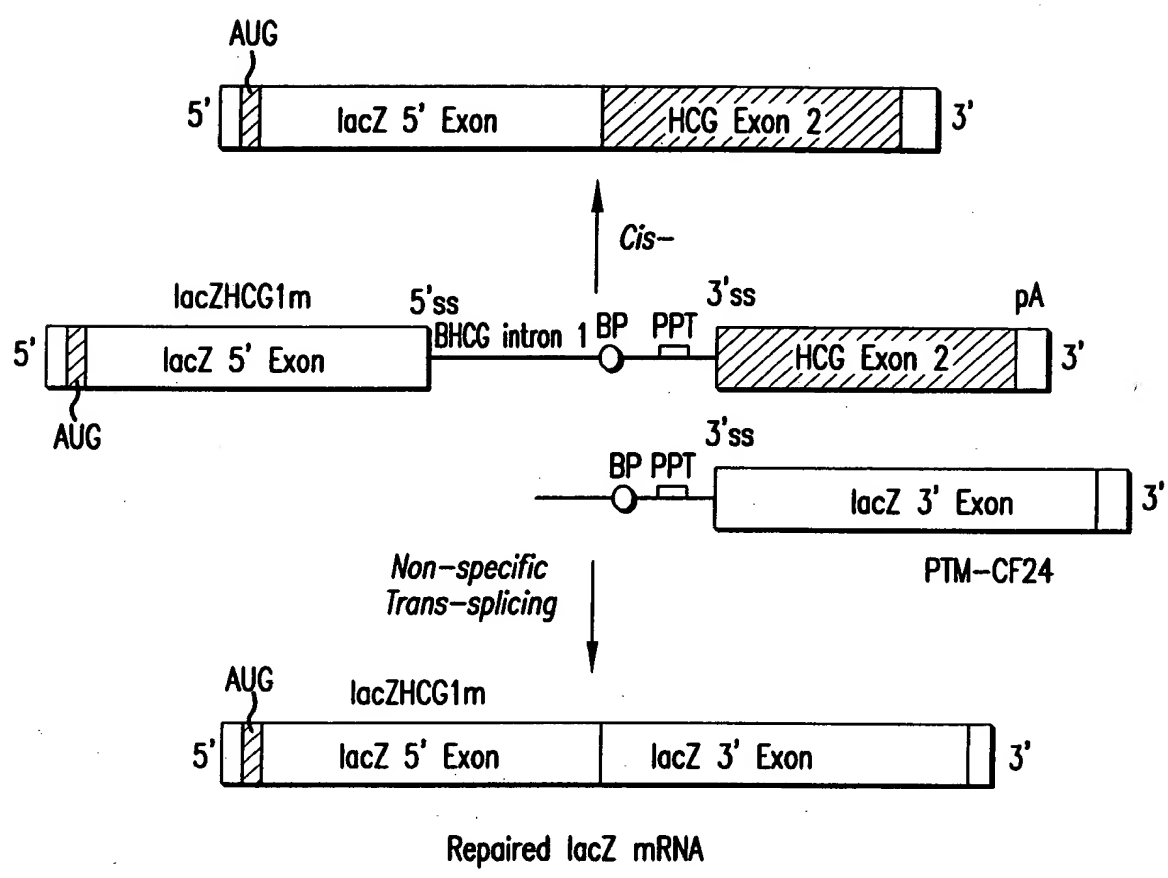


FIG.41A

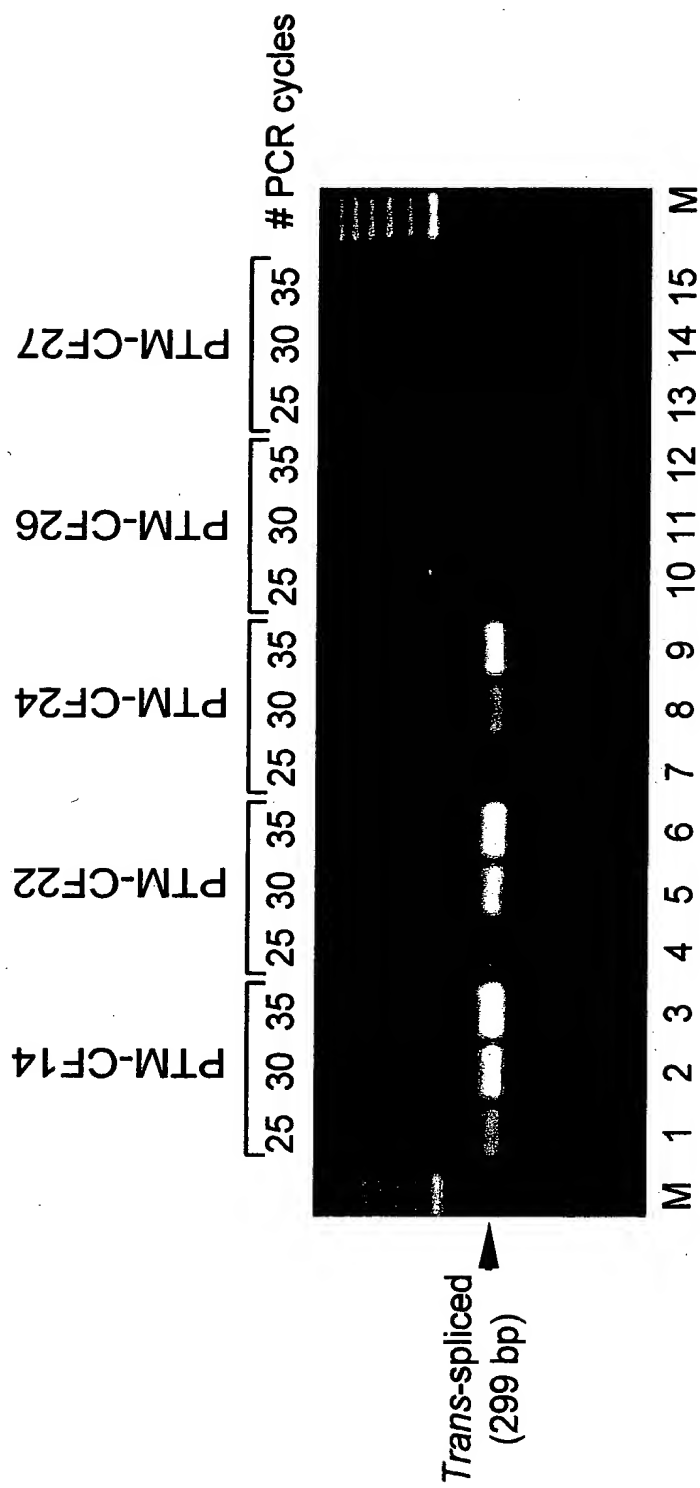


FIG.41B

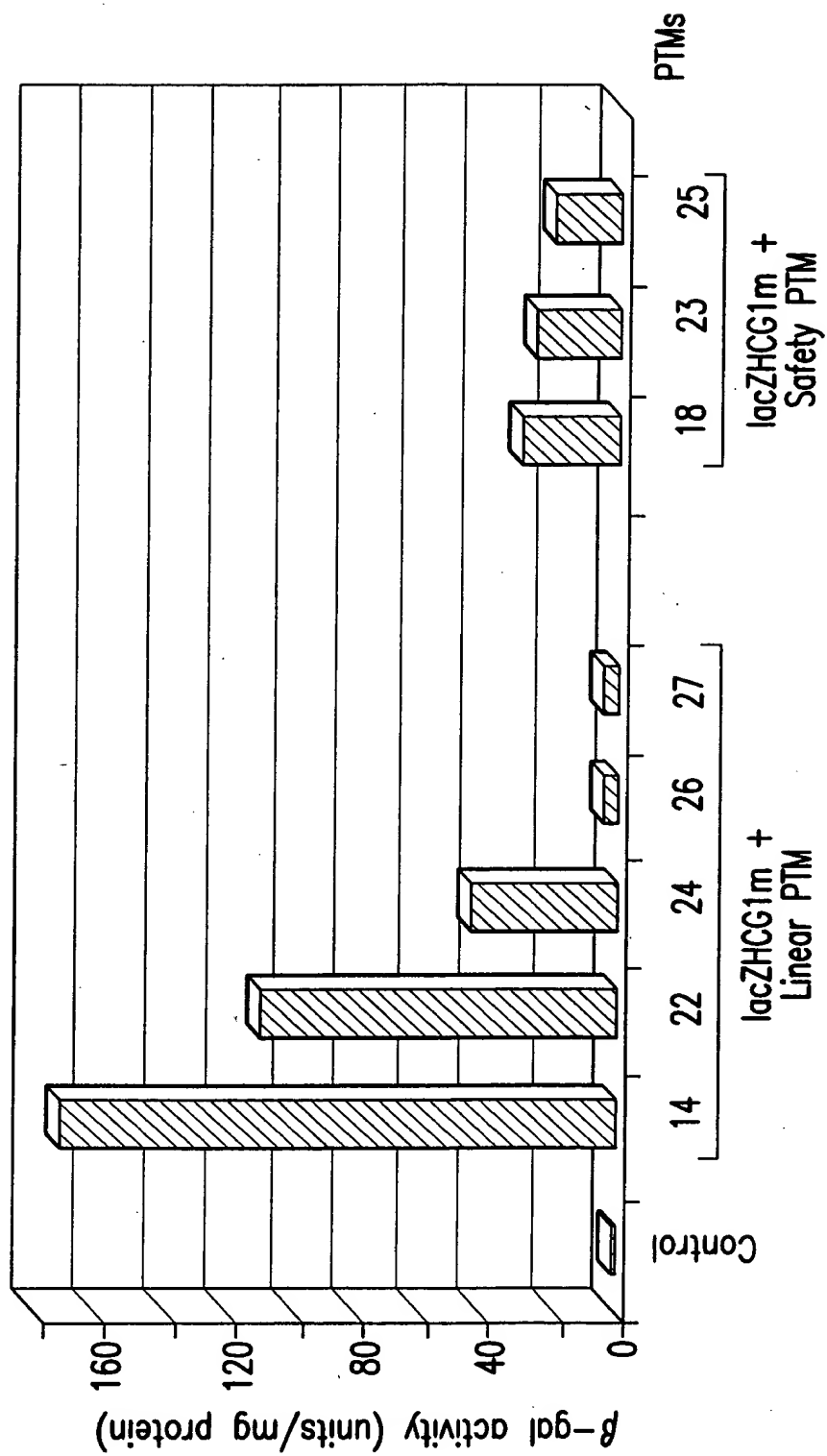


FIG.41C



Exons

1-10

ATGCAGAGGTCGCCTCTGGAAGGCCAGCGTTGTCTCCAACTTTTTTTCAGCTGGACCAGACCAATTTTGAGGAAAG
GATACAGACAGCGCCTGGAATTGTCAGACATATACCAAATCCCTTCTGTTGATTCTGCTGACAATCTATCTGAAAAATT
GGAAGAGAATGGGATAGAGAGCTGCCTTCAAAGAAAAATCCTAAACTCATTAAATGCCCTTCGGCGATGTTTTTCTGG
AGATTTATGTTCTATGGAATCTTTTATATTTAGGGGAAGTCACCAAAGCAGTACAGCCTCTCTTACTGGAAGAATCA
TAGCTTCCTATGACCCGGATAACAAGGAGGAACGCTCTATCGCGATTATCTAGGCATAGGCTTATGCCTTCTCTTTAT
TGTGAGGACACTGCTCCTACACCCAGCCATTTTGGCCTTCATCACATTGGAATGCAGATGAGAATAGCTATGTTTAGT
TTGATTTATAAGAAGACTTTAAAGCTGTCAAGCCGTGTTCTAGATAAAATAAGTATTGGACAACCTGTTAGTCTCCTTT
CCAACAACCTGAACAAATTTGATGAAGGACTTGCATTGGCACATTTCTGTGGATCGCTCCTTTGCAAGTGGCACTCCT
CATGGGGCTAATCTGGGAGTTGTTACAGGCGTCTGCCTTCTGTGGACTTGGTTTCTGATAGTCCTTGGCCTTTTTTCAG
GCTGGGCTAGGGAGAATGATGATGAAGTACAGAGATCAGAGAGCTGGGAAGATCAGTGAAAGACTTGTGATTACCTCAG
AAATGATCGAGAACATCCAATCTGTTAAGGCATACTGCTGGGAAGAAGCAATGGAAAAATGATTGAAAACTTAAGACA
AACAGAAGTAAAGTACTCGGAAGGCAGCCTATGTGAGATACTTCAATAGCTCAGCCTTCTTCTTCTCAGGGTTCTTT
GTGGTGTTTTTATCTGTGCTTCCCTATGCACTAATCAAAGGAATCATCTCCGAAAATATTCACCACCATCTCATTCT
GCATTGTTCTGCGCATGGCGGTCACTCGGCAATTTCCCTGGGCTGTACAAACATGGTATGACTCTCTTGGAGCAATAAA
CAAAATACAGGATTTCTTACAAAAGCAAGAATATAAGACATTGGAATATAACTTAACGACTACAGAAGTAGTGATGGAG
AATGTAACAGCCTTCTGGGAGGAGGATTTGGGAATTATTTGAGAAAGCAAAACAAACAATAACAATAGAAAACTT
CTAATGGTGATGACAGCCTCTTCTTCAAGTAATTTCTCACTTCTTGGTACTCCTGTCTGAAAGATATTAATTTCAAGAT
AGAAAGAGGACAGTTGTTGGCGGTTGCTGGATCCACTGGAGCAGGCAAGACGAGCTTGCTCATGATGATCATGGGCGAG
TTAGAACCAAGTGAAGGCAAGATCAAACATTCCGGCCGCATCAGCTTTTGCAGCCAATTGAGTTGGATCATGCCCGGT
CCATCAAGGAGAACATAATC77CGGCGTCAGTTACGACGAGTACCGCTATCGCTCGGTGATTAAAGCCCTGTCAGTTGGA
GGAG

Trans-splicing domain

GTAAGATATCACCGATATG-TGTCTAACCTGATTTCGGGCCTTCGATACGCTAAGATCCACCGG
TCAAAAAGTTTTACATAATTTCTTACCTCTTCTTGAATTCATGCTTTGATGACGCTTCTGTATCTATATTCATCATTG
GAAACACCAATGATATTTCTTTAATGGTGCCTGGCATAATCCTGGAAAAGTATAACACAATGAAATTTCTTCCACTGT
GCTTAATTTTACCCTCTGAATTTCTCCATTTCTCCATAATCATCATTACAAGTGAAGTCTGGAAATAAAACCCATCATT
ATTAAGTCAATATCAAATCAGGCT

FIG.42



153 bp PTM24 Binding Domain:

Nhe I

153 bp BD underlined

GCTAGC-AATAATGACGAAGCGCCCTCAGGCTCAGGATTCACTTGCCTCCAATTATCATCCTAAGCAGAAGTGATATA

TTCTTATTGTAAAGATTCTATTAACTCAATTGATTCAAATAATTTAAATACTTCTGTTTCACTACTCTGCTATGTC

Sac II

AC-CCGCGG

FIG. 43A

2003-11-24
11:13:11
2003-11-24
11:13:11
2003-11-24
11:13:11

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Trans-splicing domain

AATAATGACGAAGCCGCCCTCAGGCTCAGGATTCACCTGGCCCTCCAATTATCATCCTAAGCAGAAGTGATATTCTTA
TTTGTAAGATTCTATTAACCTATTGATTCAAAATATTTAAATACTTCCTGTTTCACCTACTCTGCTATGCACCCGC
GGAACATTATTATAACGTTGCTCGAATACTAAGTGGTACCTCTCTTTTTTTTGATATCCTGCAG

Exons 10-24

ACTTCACCTTCTAATGATGATTATGGGAGAACTGGAGCCTTCAGAGGGTAAAATTAAGCACAGTGAAGAATTTCACTCT
GTTCTCAGTTTTCTGGATTATGCCTGGCACCATTAAAGAAAATATCATCTTTGGTGTTCCTATGATGAATATAGATA
CAGAAGCGTCATCAAAGCATGCCAACTAGAAGAGGACATCTCCAAGTTGCAGAGAAAGACAATATAGTTCTTGGAGAA
GGTGAATCACACTGAGTGGAGGTCAACGAGCAAGAATTTCTTTAGCAAGAGCAGTATACAAAGATGCTGATTGTATT
TATTAGACTCTCCTTTTGGATACCTAGATGTTTTAACAGAAAAAGAAATTTGAAAGCTGTGCTGTAACTGATGGC
TAACAAAAGTAGGATTTTGGTCACTTCTAAAATGGAACATTTAAAGAAAGCTGACAAAATATTAATTTTGCATGAAGGT
AGCAGCTATTTTTATGGGACATTTTCAGAACTCCAAAATCTACAGCCAGACTTTAGCTCAAACTCATGGGATGTGATT
CTTTGACCAATTTAGTGCAGAAAGAAGAAATTCATCTAACTGAGACCTTACACCGTTTCTCATTAGAAGGAGATGC
TCCTGTCTCCTGGACAGAAACAAAAACAATCTTTTAAACAGACTGGAGAGTTGGGGAAAAAGGAAGAAATTTCTATT
CTCAATCCAATCAACTCTATACGAAAATTTCCATTGTGCAAAAGACTCCCTTACAAATGAATGGCATCGAAGAGGATT
CTGATGAGCCTTTAGAGAGAAGGCTGTCTTAGTACCAGATTCTGAGCAGGGAGAGGGGATACTGCCTCGCATCAGCGT
GATCAGCACTGGCCCCACGCTTCAGGCACGAAGGAGGCAGTCTGTCTGAACCTGATGACACACTCAGTTAACCAAGGT
CAGAACATTCACCGAAAGACAACAGCATCCACACGAAAAGTGTACTGGCCCCCTCAGGCAAACTTGACTGAAGTGGATA
TATATTCAAGAAGGTTATCTCAAGAAACTGGCTTGAAATAAGTGAAGAAATTAACGAAGAAGACTTAAAGGAGTGCTT
TTTTGATGATATGGAGAGCATACCAGCAGTGACTACATGGAACACATACCTTCGATATATTACTGTCCACAAGAGCTTA
ATTTTGTGCTAATTTGGTGCTTAGTAATTTTCTGGCAGAGGTGGCTGCTTCTTTGGTGTGCTGTGGCTCCTTGGAA
ACACTCCTCTTCAAGACAAAGGAATAGTACTCATAGTAGAAATAACAGCTATGCAGTGATTATCACCAGCACCAGTTC
GTATTATGTGTTTTACATTTACGTGGGAGTAGCCGACACTTTGCTTGCTATGGGATTCTTCAGAGGTCTACCACTGGTG
CATACTCTAATCACAGTGTGAAAATTTTACACCACAAAATGTTACATTCTGTTCTTCAAGCACCTATGTCAACCCTCA
ACAGCTTGAAAGCAGGTGGGATTCTTAATAGATTCTCCAAAGATATAGCAATTTGGATGACCTTCTGCCTCTTACCAT
ATTTGACTTCATCCAGTTGTTATTAATTGTGATTGGAGCTATAGCAGTTGTCCGAGTTTACAACCTACATCTTTGTT
GCAACAGTGCCAGTGATAGTGGCTTTTATTATGTTGAGAGCATATTTCTTCCAAACCTCACAGCAACTCAAACAAGTGG
AATCTGAAGGCAGGAGTCCAATTTTCACTCATCTTGTACAAGCTTAAAGGACTATGGACACTTCGTGCCTTCGGACG
GCAGCCTTACTTTGAAACTCTGTTCCACAAAGCTCTGAATTTACATACTGCCAACTGGTTCTGTACCTGTCAACACTG
CGCTGGTTCCAAATGAGAATAGAAATGATTTTGTATCTTCTTCAATTGCTGTTACCTTCATTTCCATTTTAAACAAG
GAGAAGGAGAAGGAAGAGTTGGTATTATCTGACTTTAGCCATGAATATCATGAGTACATTGCAGTGGGCTGTAAACTC
CAGCATAGATGTGGATAGCTTGATGCGATCTGTGAGCCGAGTCTTTAAGTTTATTGACATGCCAACAGAAGGTAAACCT
ACCAAGTCAACCAAAACCATACAAGATGGCCAACTCTCGAAAGTTATGATTATTGAGAATTCACACGTGAAGAAAGATG
ACATCTGGCCCTCAGGGGGCCAAATGACTGTCAAAGATCTCACAGCAAAATACACAGAAGGTGGAAATGCCATATTAGA
GAACATTTCTTCTCAATAAGTCTGGCCAGAGGTGGGCCTCTTGGGAAGAACTGGATCAGGGAAGAGTACTTTGTTA
TCAGCTTTTTTGAGACTACTGAACACTGAAGGAGAAATCCAGATCGATGGTGTGCTTGGGATTCAATAACTTTGCAAC
AGTGGAGGAAAGCCTTTGGAGTGATACCACAGAAAGTATTTATTTTTCTGGAACATTTAGAAAAAAGTGGATCCCTA
TGAACAGTGGAGTGATCAAGAAATATGGAAGTTGCAGATGAGTTGGGCTCAGATCTGTGATAGAACAGTTTCTTGGG
AAGCTTGACTTTGTCTTGTGGATGGGGCTGTGTCTTAAGCCATGGCCACAAGCAGTTGATGTGCTTGGCTAGATCTG
TTCTCAGTAAGGCGAAGATCTTGCTGCTTGATGAACCCAGTGCTCATTGGATCCAGTAACATACCAATAATTAGAAG
AACTCTAAAACAAGCATTGTCTGATTGCACAGTAATTTCTGTGAACACAGGATAGAAGCAATGCTGGAATGCCAACAA
TTTTTGGTCAAGAAGAGAACAAGTGGCGCAGTACGATTCCATCCAGAACTGCTGAACGAGAGGAGCCTCTTCCGGC
AAGCCATCAGCCCCTCCGACAGGGTGAAGCTCTTTCCACCGGAAGTCAAGCAAGTGAAGTCTAAGCCCCAGATTGC
Histidine lag Stop
TGCTCTGAAAGAGGAGACAGAAGAAGAGGTGCAAGATACAAGGCTTCATCATCATCATCATATTAG

FIG.43B

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